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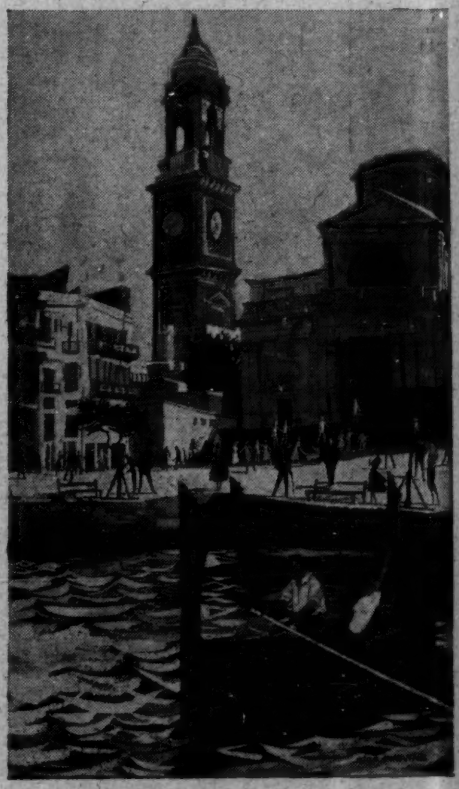

BRITISH MEDICAL JOURNAL

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CORONARY ARTERY DISEASE*

BY

Sir HOWARD FLOREY, M.D., F.R.C.P., F.R.S.

Professor of Pathology, University of Oxford

[WITH SPECIAL PLATE]

When I could no longer hide the title of this lecture from members of my laboratory one of my colleagues remarked bluntly, "You have been foolhardy." This is unfortunately true, and the force of the remark was further borne in on me when I read an admirable review entitled *Lipids in Relation to Arterial Disease* by Hilditch and Jasperson (1959). They said: "Faced with a problem of such extreme complexity—involving possibly not only dietary fat but also protein, and into which perhaps endocrine metabolism as well as enzyme metabolism and their possible disorders, and other factors such as sex, heredity, nervous strain, sedentary or mobile occupations, and so on may enter—it seems to us both unfortunate and surprising that some medical investigators have been rather prone to seize on one or other facet of the problem and thereon to formulate hypotheses incongruous with the slender weight of the experimental findings on which they are based."

I will try to set out as clearly as I can some of the pathological changes involved in coronary artery disease, to mention some of the theories on their origin, and then lead on to discuss how more progress might be made in the examination of the changes in a very common disease which is often associated with crippling effects on the cardiac muscle or sudden death. Therapeutic measures will also be mentioned.

Components of Coronary Disease

There are two separate but probably associated components of coronary artery disease—namely, alterations in the wall of the artery itself and alterations in the content of the artery.

First let us consider the wall of the artery. Electron microscopy makes it possible to obtain a clearer idea of the intima of the coronary artery, in which it is supposed the initial lesions of atherosclerosis occur. It has so far not proved possible to obtain good human material, but there is little reason for supposing that much difference exists between human and pig arterial tissue. The figure was obtained from the pig. It shows that the artery is lined by a single layer of endothelial cells, which at this magnification are structures of considerable size, and that these together form a continuous cellular barrier between the lumen of the artery and the tissue of the intima There is scarcely any space between the cells at their junctions, certainly not a substantial amount of cement as is still commonly believed to exist between endothelial cells.

How substances are transported through this cellular barrier is a problem common to all endothelium, and it has not yet been solved. The properties of endothelium deserve more attention than is usually accorded to them, for through this layer of cells all nutrients and fluids reaching the intima and immediately subjacent media have to pass. Below the endothelium is a layer in which collagen, elastic tissue, and some other fine fibres can be seen. They are probably embedded in a mucoprotein matrix which does not show in electron micrographs. Outside this layer the intima is bounded by a fenestrated elastic tissue membrane. (No fenestrae are shown in the Special Plate.) In the fenestrae smooth muscle cells, such as are present in the media, sometimes occur. It is quite possible that the scattered cells normally encountered in the intima are smooth muscle cells and not fibroblasts or macrophages.

Developed Lesions in Man

Before attempting to inquire what are the initial changes of atheroma it may be profitable to consider what can be present in fully developed lesions. The constituent of the intimal thickening or plaque which has attracted most attention is lipid. This material may be free in the tissues or inside cells which are usually considered to be macrophages but which could be smooth-muscle cells. Lipid may also be found in the neighbouring media. At the base of the intimal plaque a semi-fluid mass of lipid and cholesterol crystals may be present. It is this which has given the name atheroma to the lesion. Considerable amounts of calcium may be encountered as well as fibres usually regarded as collagenous and elastic in nature. Eventually there may be vascularization, ulceration, and haemorrhage into the plaque. The intimal thickenings may be of great variety, eccentric or fairly evenly spread around the lumen; the fibrous component may be most conspicuous in some lesions but in others the lipid. The central problem is to explain why these constituents appear at discrete points in the coronary arteries.

It has been known for over a century that there is a considerable amount of cholesterol in the lipid that accumulates in atherosclerotic lesions. Indeed, the public is now aware of cholesterol and its putative connexion with the development of atherosclerosis. For example, there was, not long ago, a large advertisement in *The Times* asking, "How's your cholesterol?" and urging us to eat more fish to lower its level; and, again, a very penetrating cartoon in the *New Yorker* in which a woman at a cocktail party inquires, "Are you a no-cholesterol doctor or are you one of those no-cholesterol-is-all-bosh doctors?" This cartoon represents fairly the confusion that exists about the relationship of lipids to the genesis and development of atherosclerosis.

*The Jephcott Lecture delivered at the Royal Society of Medicine on May 9, 1960.

Evidence Other than Morbid Anatomical for the Involvement of Lipids

What are the reasons, beside the morbid anatomical findings, to connect errors of lipid metabolism with atherosclerosis ?

There is considerable evidence of some relationship between the amount of lipid in the blood, the severity of atheromatous lesions, and the incidence of coronary thrombosis. Thus it has been found that some races which have a low incidence of coronary thrombosis live on diets with a low fat content. They have a low level of cholesterol in the blood, and a cholesterol/phospholipid ratio of about one. There is also a relatively low concentration of β-lipoprotein. Many patients who have coronary heart disease have a higher mean cholesterol level in their serum than so-called normals, a high concentration of β-lipoproteins, and a cholesterol/phospholipid ratio greater than one. It is generally agreed that patients with diabetes mellitus, myxoedema, and familial hypercholesterolaemia, in whom raised serum cholesterol levels and other abnormalities of the lipid occur, have a high incidence of atherosclerosis. Nevertheless, many patients with atherosclerosis do not show such abnormalities of serum lipids.

Interest is now moving to a detailed comparison of the composition of serum lipids with that of the lipids occurring in plaques, a comparison made possible by spectacular improvements in methods of chemical analysis. Most of the work has been done on aortic material. It may well be that the lipid content of coronary lesions and those of the aorta are similar, but they are not identical. For example, it was recently shown that triglycerides formed 50% or more of the total lipids in some lesions of the coronary arteries, which is very much more than in aortic lesions, while cholesterol esters and free cholesterol were proportionately less.

So far as aortic lesions are concerned the percentage of total lipids in the lesions increased with increasing severity of the lesions, and cholesterol and its esters increased more markedly than the phospholipids (Böttcher, Keppler, Romeny-Wachter, Boelsma-van Houte, and Van Gent, 1958; Böttcher, Woodford, Romeny, Boelsma, and Van Gent, 1959). In view of the importance that has been attributed to polyunsaturated fatty acids such as linoleic and arachidonic acids it is well to note that at all stages the cholesterol ester fatty acids were mainly unsaturated, oleic acid constituting about 40% and linoleic acid 25% of the total fatty acids. With increasing severity of the lesions the proportion of unsaturated fatty acids in this fraction actually increased.

The lipids contained in atherosclerotic plaques are apparently qualitatively the same as those circulating in the blood. Hence a very commonly accepted view of the formation of an atherosclerotic patch is as follows.

Lipids circulate in the plasma mainly in the form of α- and β-lipoproteins. The α-lipoproteins are maintained at a relatively steady level in the blood, and it is the β-lipoproteins, which have the larger molecule, that are increased in amount when the cholesterol level of the blood is raised. The β-lipoproteins are rather ill-defined substances, composed of protein, cholesterol, phospholipids, and fatty acids. It is supposed that in the atheromatous artery the β-lipoproteins in the blood pass through the endothelial layer in greater amount than normal. Our ignorance of the mechanism by which substances pass through endothelium is profound, but the mechanism could be of great importance in connexion with this theory of atherogenesis. At all events, it is supposed that lipid passes in some way through the endothelium and reaches the subendothelial space, which is shown, highly magnified, in the Special Plate. In this space something happens so that the rather unstable lipoproteins are broken down, with the liberation of cholesterol, fatty acids, and phospholipids. In this connexion a recent observation of Kayahan (1959) may be pertinent. In investigating the excess fat in atherosclerotic intimas he obtained evidence that globulins from atherosclerotic intimas could bind considerably more lipid than globulins from normal intimas.

Some fatty acids, phospholipids, and protein pass on through the tissue spaces of the media into the lymph vessels in the adventitia and so are removed, but cholesterol, both as free cholesterol and as esters, is relatively insoluble and so tends to stop in the intima. Thus cholesterol and a certain amount of phospholipid are left behind. Compared with the composition of serum lipids the phospholipid in the plaque is less in proportion to the cholesterol; in other words, the phospholipid/cholesterol ratio is lower. Under this theory of the mechanism of atherogenesis this insoluble residue is the initial lesion. With the passage of time it increases in amount, macrophages appear, fibrous tissue develops, and so on, until plaques containing much lipid and fibrous material are built up. Under this theory the lipid is directly derived from the plasma. The calcium salts which are often prominent must also come from the same source.

What I have just outlined is a relatively simple theory associating the content of cholesterol and other lipids in the blood with the accumulation in the arterial wall. Such a view is plausible, and indeed many pathologists would say that there was evidence that the earliest lesion in the formation of an atherosclerotic plaque was a "fatty streak" or a collection of lipid just beneath the endothelium. On the other hand, there are pathologists who maintain that the so-called fatty streaks which can be seen in the aortas of even very young people have nothing to do with the development of the serious lesion of later life.

Great attention has been given to dietary lipids in the belief that these substances may in some way determine the deposition of fats in the intima of arteries, but it should be mentioned that some observers think that the protein content of the diet is of great importance (possibly as important as the lipid content) in controlling serum lipid levels (Kokatnur and Kummerow, 1959). If this should be true, clearly some present-day views on the atherogenic properties of "western" diet would have to be considerably recast.

There is also the possibility that the lipid is formed by the activity of cells in the vessel wall. Phospholipid can certainly be synthesized there, and a recent note on an examination of human aortic and coronary lesions with the electron microscope states boldly that the fat is intracellular and is found especially in smooth muscle. The suggestion is made that the accumulation of fat in atherosclerotic lesions is the result of metabolic processes in the cells of the arterial wall (Geer, McGill, Strong, and Holman, 1960).

I have briefly mentioned only a small fraction of the very large amount of work on the association of the

lipid content of the blood and atherosclerosis, but even if I had time to review more evidence I should still say that on the whole the observations do not carry complete conviction that an increased level of blood lipids is the primary cause of atherosclerosis, though it may well be important in the development of the lesions.

Elastic Tissue

But there are other structural changes in atherosclerosis besides the accumulation of lipids.

A number of workers have demonstrated that from birth onwards progressive changes can be shown in the elastic tissue of the intima of the coronary arteries. At birth the internal elastic lamina appears in a section as a smooth corrugated continuous membrane, but even during infancy this tends to fragment and to reduplicate, so that by the end of the second decade the intima may have thickenings in which elastic tissue is prominent. This is so usual that it must be considered to be a normal part of development.

It is conceivable that the mechanical stresses of the circulation, especially at branchings of the vessels, may put a constant strain on arterial tissue, especially the elastic fibres. At junctions, eddies in the blood-stream are likely to form, and these eddies may set up high-frequency vibration which might produce obvious damage after many years. It is certainly true that lipid deposits can often be seen first in relation to elastic-tissue fibres.

It could be that mechanical damage to the arteries might in this way initiate lesions, and this should be very seriously considered, for the patchy distribution of atherosclerosis must be explained. There is a possibility that mechanical damage to the arterial wall may favour the deposition of lipid from the blood. Colour is lent to this supposition by the experiments of Waters (1957), who made use of the fact that he could damage the walls of the coronary arteries of dogs by the administration of allylamine. If lipoprotein in considerable amounts was injected into the blood-stream lipid accumulated at the sites of damage in the coronaries, and the structure of resulting lesions bore some resemblance to the human lesion.

Ground Substance

There is one other constituent of the intima which we have not considered, and that is the ground substance which stains metachromatically with such dyes as toluidine blue. Through this ground substance, which probably contains mucopolysaccharide, everything which leaves the lumen of the vessel has to pass. There is no reason why the primary lesion should not be due to some change in it, but the evidence for such a change is very small. It can be said, however, that in well-developed atherosclerotic lesions the amount of stainable ground substance may be increased.

Changes in Blood

We have so far considered changes occurring in the wall of the coronary artery. What about changes in the blood circulating in the artery?

There is sometimes confusion between clotting and thrombosis. Thrombosis, according to current information, is initiated by the deposition of platelets on the wall of a vessel in which blood is flowing—probably a damaged wall. These deposits build up, entangle white corpuscles, and entrap red cells. With growth of the thrombus fibrin appears, but this is not an initial constituent. Thus a thrombus is an intravascular object with a characteristic structure, whereas a clot is formed by fibrin, which entangles the blood constituents in its immediate vicinity. Clots similar to those forming *in vitro* may form in blood made stagnant by the blocking of a vessel with a thrombus, and so they may be of importance, though secondary, in coronary thrombosis. The mention of coronary thrombi usually conjures up a picture of the final complete blocking of the affected artery, but Duguid (1946, 1948, 1949) and his colleagues have produced weighty evidence in favour of a theory, put forward by Rokitansky in the eighteen-forties, to the effect that at an early stage the lesion of atheroma is due to the deposition of fibrin on the inside of a vessel wall. Subsequently the deposit becomes incorporated in the wall.

Few would, I think, now deny that the organization of mural thrombi or deposits of fibrin plays an important part in the enlargement of atherosclerotic plaques on which they occur, but many are not convinced that mural thrombosis or deposition of fibrin explains the initial lesions. It is, for example, impossible to derive the amount of lipid present in plaques from breakdown products of red cells or other constituents contained in a thrombus of suitable size. But even if we only agree that mural thrombosis adds to lesions already existing it becomes a very important process, and our attention is concentrated not only on the state of the wall but on the state of the blood circulating in the vessel.

Epidemiological studies by Morris (1951), combined with the examination of the records of necropsies carefully conducted many years ago, indicate that it is an increase of thrombosis and cardiac infarction which is the feature of the present time and not an increase in atherosclerosis. If this is indeed the case you will note that such a view appears to be incompatible with Duguid's theory, for if more thrombosis is occurring to-day than formerly and mural thrombosis is a cause of atherosclerosis, then atherosclerosis should be much more frequent to-day than it was. This does not appear to be so.

Many attempts have been made to show that the blood of atherosclerotics clots more easily than that of so-called normals. Even if this were so it would not show that it was more apt to deposit a thrombus in a vessel, for this depends on alterations to platelets. In this connexion McDonald (1960) has found that patients suffering from ischaemic heart disease have abnormally sticky platelets as judged by an *in vitro* test. This work needs to be confirmed and extended, and the relationship between platelet stickiness *in vitro* and a tendency to thrombosis in the body requires further exploration before such findings can be definitely related to disease in man.

The relationship between lipids and blood-clotting has been investigated extensively, but there has been much controversy over many of the findings, and comparatively few facts are established in such a manner as to command general agreement. At the present time not enough is known about the connexion between blood coagulation in a test-tube and thrombosis in the body to assess the likelihood that these findings are of pathological significance.

If fibrin formation is important in human arterial disease, not only clotting but the converse process of

fibrinolysis may be important. It has been known for a long time that blood may develop fibrinolytic activity after injury, severe exercise, or emotional stress. Eight years ago it was discovered that all human blood shows a labile fibrinolytic system, provided that the blood is rapidly cooled after collection (Fearnley, Revill, and Tweed, 1952; Truelove, 1953; Fearnley and Tweed, 1953), and it has been claimed that this labile fibrinolytic system is partly inhibited after a fatty meal. Recently this claim has been denied (Greig, 1956; Greig and Runde, 1957; Nitzberg, Peyman, Goldstein, and Proger, 1959; Billimoria, Drysdale, James, and Maclagan, 1959; Hougie and Ayers, 1960). The methods used by the different investigators were not the same, so the apparent confusion may turn out to be methodological. At present, however, the position is far from clear.

The belief that atheromatous plaques may be derived from thrombi has naturally led to attempts to demonstrate fibrin in them. Here conventional staining methods are not of much use. Levene (1955) showed that atheromatous plaques contained a fibrous protein whose appearance in the electron microscope resembled that of fibrin. Crawford (1960) and his colleagues have attacked the problem by using fluorescent anti-fibrin antibodies and have been able to show specific fluorescence in plaques. Indeed, Crawford and Wolff (1960) showed such fluorescence in aortic intimal fatty streaks. Possibly fibrin might be formed in plaques *post mortem*, for the endothelium rather quickly disintegrates and plasma might seep in and clot in the intima. In short, the evidence that atheromatous plaques contain fibrin is suggestive but not as yet conclusive.

Animal Experiment

Can we learn anything more definite about the origin and development of atherosclerosis by animal experiment? One always hopes by such means to isolate the essential factors in a problem and so simplify the understanding of the phenomena involved.

Some 50 years ago Anitschkow and Chalatow discovered that if rabbits were fed a diet containing considerable amounts of cholesterol they developed lesions in the intima of their aortae which bore some resemblance—they thought a close one—to those occurring in man. The level of cholesterol in the serum of rabbits may rise to as much as 1,000 mg. per 100 ml. or even more.

How does the lipid material which is thus in great excess in the blood gain access to the intima of the vessel? I think it is clear in some of this rabbit material that the endothelial cells over well-developed plaques, but not elsewhere, contain considerable amounts of sudanophil substance in their cytoplasm, but it cannot be said whether this is lipid in transport to the intima (Poole and Florey, 1958).

If the lipid does not pass directly through endothelium, are there other possibilities?

One of the features of the rabbit lesion is the presence of large numbers of lipid-laden macrophages. Macrophages filled with lipid can be found in passage through the endothelium, but of course it is not at all certain in which direction they are going; they might be going either outwards or inwards. But macrophages containing lipid have been demonstrated in the circulating blood of cholesterol-fed rabbits by Rannie (1959), and many observers have seen that macrophages may be present on the endothelial surfaces of such plaques. Poole and I believe that if the macrophages which come to rest on the surface go into the plaque they do so by penetrating the endothelium, as Leary (1941), who considered that the macrophages arise in the liver, was the first to suggest. Rannie and Duguid (1953), on the other hand, believe that the macrophages adhere to the surface and endothelium then grows over them, and that thus the macrophages are incorporated in the plaque.

There is no evidence, so far as I am aware, that macrophages transport lipid in human atherosclerosis in the way postulated for the rabbit lesion. Moreover, in the cholesterol-fed rabbit there is a large deposit of cholesterol in the liver and spleen and in phagocytic cells generally throughout the body. The rabbit disease is, in fact, a cholesterolosis. When cholesterol feeding is continued for some time the lesions produced in the rabbit's aorta resemble those which are found in man in that they contain fibrous tissue and free lipid in the base of the lesion.

By feeding cholesterol in large amounts similar lesions can be produced in chickens, and a great deal of work has been devoted to studying the influences which affect the deposition of this cholesterol. It has also been found possible to produce lesions in dogs, monkeys, and rats, but cholesterol feeding alone is insufficient. Auxiliary methods to raise the level of blood cholesterol have to be employed.

None of the experimental lesions mentioned are accompanied in the ordinary course of events by ulceration, haemorrhage, or thrombosis. Suggestive as these experiments are, it must be confessed that they leave much to be desired. Nevertheless, there is no doubt that they have been taken to strengthen the view that a high blood cholesterol is responsible for the genesis of human atherosclerosis.

Naturally Occurring Atherosclerosis in Animals

Recently, increasing interest has been taken in naturally occurring atherosclerosis in species other than man. For example, some very interesting observations have been made on pigeons by Clarkson, Prichard, Netsky, and Lofland (1959), who discovered that certain breeds regularly developed lesions in their aortae, and that the lesions bore a very close resemblance to those in man. They sometimes broke down, with the production of a porridge-like material as in human lesions. They sometimes ulcerated, with thrombus formation on the surface.

This condition is particularly important in that it occurs in the absence of special dietary procedures, and only in certain breeds of pigeon. Other breeds do not show it when kept under comparable conditions. In other words, there seems to be a very strong genetic element in the development of this particular atherosclerotic lesion. The pigeons, whether they bore lesions or not, had the relatively high blood cholesterol of, for example, around 350 mg. per 100 ml. (Lofland and Clarkson, 1959).

The baboon has also attracted attention. Lindsay and Chaikoff (1957) found lesions in two zoo baboons, and Gillman and Gilbert (1957) described lesions resembling those in man in the aortae of baboons in the laboratory. The lesions developed in the presence of low concentrations of cholesterol in the blood, and indeed this level sank with age. It has since been discovered that baboons living in the natural state in Kenya, and probably on a fat-poor diet, occasionally

develop fatty streaks, and, more rarely, fibrous plaques in the aortae (McGill, Strong, Holman, and Werthessen, 1960). At present baboons are being examined in a colony which is being raised in Texas. So far nothing new about the causation of the initial atherosclerotic lesion has emerged from these studies, but clearly the baboon, although intrinsically difficult to deal with, may have possibilities for future research.

Farm animals, and perhaps also those in the wild, seldom survive to biological old age, and little is known about the frequency of such changes in old animals. Recently Jennings, Stehbens, French, and I have had an opportunity to examine the vessels of a pig which reached the mature age of 7 years and 4 months, which is slightly past middle life for a pig (Burrow, personal communication). This pig had an isolated pyloric pouch which had secreted mucoid juice for seven years, but there is no reason to connect the arterial lesions with the events in the pylorus. At post-mortem examination the aorta and coronary arteries showed atherosclerotic lesions which bore a striking resemblance to partly developed lesions in man, and there were elastic-tissue changes in the coronary and cerebral vessels similar to those which occur with advancing age in man. Of particular interest is the fact that plaques and diffuse fat-containing intimal thickenings were present in the first few centimetres of the coronary arteries before they entered the muscle; many of the plaques were at bifurcations. Elastic and collagenous tissue, smooth-muscle fibres, and deposits of fat and of calcium were present in the coronary and aortic plaques, though there was no definite softening and no ulceration, haemorrhage, or vascularization (Jennings, Florey, Stehbens, and French, 1961).

It might not be going too far to believe that the same factors were operating to produce the lesions in the pig as are present in man. For at least the last three years of its life the pig was on a fat-poor diet.

There are in the literature some other indications that the pig may be a suitable animal for experiment because naturally occurring aortic plaques, albeit small, increase in frequency with age even in quite young pigs. Commercial pigs seldom live to be much more than 3 years old, but lesions were found in over 30% in the oldest group of a series obtained from the slaughterhouse (Gottlieb and Lalich, 1954). An increase of lesions has been described in young pigs after feeding with butter, though others have not found this effect (Rowsell, Downie, and Mustard, 1958).

The pig, like man, is omnivorous, and it is said to have a similar cardiovascular system and metabolism to that of man—whatever that may mean precisely—and the composition of the plasma lipoproteins has been said to be in some respects more like that of man than of other mammals. Different strains of pig may show consistent differences in the concentrations of serum lipids and cholesterol (Lewis and Page, 1956), so that it might be possible to choose especially suitable strains for particular purposes. I will be rash enough to suggest that in the pig we have an animal with which we might solve many of the outstanding problems of atherosclerosis. To do so would require extensive effort. It would first be necessary to demonstrate that a substantial proportion of ageing pigs show the lesion. If this should prove to be the case it would not be impossible to plan experiments which would test the many theories concerning the genesis of atherosclerosis and to evaluate critically the effects of therapy, whether they be of a dietary or other nature. I stress that ageing pigs should be used. It is perhaps worth noting here that the pigeons I mentioned previously were 7 years old.

Prevention and Treatment

The study of disease processes in man or animals not only has its intrinsic interest, but holds out the possibility that its results may be applied in human disease. So one might inquire whether the enormous number of observations and experiments already recorded have given us anything firm on which to base prevention and treatment.

If one considers that the origin of atherosclerosis is due to errors of lipid metabolism with the presence of a high cholesterol level in serum, then dietary manipulation may be of great importance. How does one set about lowering the blood cholesterol? It has been shown that it is possible to lower blood cholesterol and the β-lipoprotein level both in man and in animals by the administration of certain hormones such as oestrogens and thyroid hormones, but so far their use for this purpose has not been clearly shown to be beneficial to patients with atherosclerosis.

Of recent years it has been demonstrated by a number of workers that relatively high levels of cholesterol in the blood of man can be lowered by feeding substantial amounts of fats containing various polyunsaturated acids, such as linoleic and arachidonic and other acids contained in menhaden oil (Ahrens *et al.*, 1959). Why does the level of blood cholesterol sink? Is the cholesterol metabolized and got rid of from the body in some form, or is it merely removed from the blood and stored somewhere, perhaps even in the arterial wall, or is there a diminution of the endogenous production of cholesterol? There is some evidence from patients with biliary fistulae that excretion in the bile of cholic acid, which can be derived from cholesterol, is greatly increased after the ingestion of sunflower-seed oil—an oil rich in polyunsaturated fatty acids—or after the intravenous injection of cottonseed oil (Gordon, Lewis, Eales, and Brock, 1957; Lewis, 1958), and there is independent evidence that faecal excretion of cholesterol and its transformation products is increased after the administration of certain dietary fats containing polyunsaturated fatty acids. Thus the unsaturated fatty acids may accelerate the katabolism of cholesterol to cholic acid.

It is, however, by no means certain that lowering the level of serum lipid by the administration of polyunsaturated fatty acids has any effect on the development of atherosclerosis or on the incidence of thrombosis, and we badly need well-planned observations on a very considerable scale to settle this point.

To mobilize the lipid in plaques already fully formed seems to be an even more formidable undertaking, but perhaps it is not impossible, for recent results on natural pigeon atherosclerosis suggest that birds given polyunsaturated fatty acids in their diet for a year have less extensive lesions than pigeons not so treated (Clarkson and Lofland, 1960).

The idea that the lipid in a plaque in a coronary artery might be at least partly removed is made more hopeful by the fact that 50% may be triglyceride, and it has been shown that triglyceride is readily oxidized by macrophages (Day and Harris, 1960; Day, 1960).

Perhaps some benefit might ensue by merely preventing the accumulation of new triglyceride. Whether the fibrous material would get less is problematical—indeed, the whole proposition is problematical.

If one takes the view that mural thrombosis is all-important, clearly steps to prevent thrombus formation are of the greatest interest. A thrombus begins by the deposition of platelets around which white cells and fibrin collect. It is commonly assumed that an anticoagulant such as heparin will prevent thrombus formation, but this is not necessarily true, for Poole (1959) has found that in an *in vitro* system heparin does not affect the agglutination of platelets to form thrombi although fibrin formation is stopped. Possibly some substance which prevents platelet agglutination might be found helpful in controlling the early stages of the disease, but a substance with this property which would be harmless to the body does not, so far as I am aware, exist.

Since fibrin forms part of a thrombus it is not unreasonable to suppose that anticoagulants might be helpful in treating coronary thrombosis by preventing extension of the thrombus, but I understand that there is at present no agreement about the advantages of giving prolonged anticoagulant treatment to those who have had a coronary infarction. Other possibilities exist—for example, plasmin might be used to remove the fibrin component of a thrombus and so open up an artery again—but so far nothing practicable for human therapeutics has emerged.

Surgery

It has been said that surgeons score some of their greatest successes when unblocking tubes. A few years ago it would have sounded fantastic to suggest that it might be possible to remove material surgically from the lumen of a coronary artery, but such a procedure is now carried out. Endarterectomy is often successful in restoring circulation in large arteries such as the aorta, but smaller vessels tend to thrombose again. The operation is in what the surgeons call the experimental stage, but their efforts will be watched with great interest, and it is quite possible that future treatment of advanced coronary disease may lie with them.

Less hazardous than endarterectomy is the attempt to improve collateral circulation by putting an irritant into the pericardial sac. Small vessels form in the resulting inflammatory tissue, and at one time it was believed that they enabled blood to pass from the parietal pericardium into the heart, but now it is suggested that the new vessels only offer new anastomotic channels between the coronary arteries themselves and so facilitate a more even distribution of the blood reaching the heart.

More radical procedures to bring new blood to an ischaemic myocardium involve grafting external structures into the heart or on to its surface. Of these, perhaps the most interesting is transplantation of the mammary artery. The originator of this procedure (Vineberg, 1946, 1954; Vineberg and Miller, 1953; Vineberg, Munro, Cohen, and Buller, 1955) implanted an open mammary artery into the ventricular muscle and thought that the blood issuing from the vessel would find its way through spaces in the muscle to the ventricular chamber, and that the artery would sprout and eventually join up with the coronary arteries and so increase the blood supply to the heart. Injection of such transplanted arteries with plastic substances shows that they do eventually form connexions with the coronaries, but it does not seem at all probable that the mammary artery sprouts fully differentiated arteries which join up with ventricular arteries. Some light has been thrown on the possible mechanism involved in the development of the additional blood supply by examining the march of events in other tissues. When a piece of duodenum is implanted subcutaneously in a rabbit, vessels from the surrounding tissue unite with vessels of the gut, but this union is accomplished by the sprouting of numerous small vessels, probably of capillary size, which join up and are then modelled to form arteries and veins which connect with the original arteries and veins (North, Sanders, and Florey, 1960).

From some experiments on implantation of mammary arteries of the pig into the ventricle we think that the vessel soon thromboses near its free end and that then small vessels, possibly from the vasa vasorum, sprout and connect with pre-existing ventricular vessels and eventually enlarge to form arteriolar connexions. After operation in man the connexions which develop between the mammary artery and the coronaries do not appear to carry a very substantial amount of blood, and this operation has not gained much currency among cardiac surgeons.

I have already taxed your patience by presenting so much that must be common knowledge to all, but I would like finally to point out the enormous change in point of view which has taken place in the last 30 or so years. Formerly atherosclerosis was thought to be a manifestation of old age about which nothing could be done. No doubt changes that we must consider to be inevitable with advancing years do play a great part, much as we may dislike that idea, but the increased incidence of coronary artery disease in young people has greatly stimulated the examination of all aspects of the disease. We are still in a state of much confusion, but if I have done anything to indicate some of the growing points of investigation I shall be very happy.

[This lecture was illustrated by many slides. It has in part been rewritten to avoid reference to them. My thanks are particularly due to Dr. M. A. Jennings and Dr. J. C. F. Poole for their assistance in preparing the lecture.]

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IMMUNOLOGICAL DIFFERENCES BETWEEN NORMAL AND MALIGNANT CELLS

BY

R. C. NAIRN, M.D., Ph.D.

H. G. RICHMOND, M.D.

M. G. McENTEGART, M.D.

AND

J. E. FOTHERGILL, Ph.D., B.Sc.

From the Departments of Pathology, Bacteriology, and Biological Chemistry, University of Aberdeen

[WITH SPECIAL PLATE]

One of the traditional concepts of malignant change is that neoplastic cells lack certain growth-controlling enzyme systems present in normal cells. On this hypothesis, normal cells should contain proteins which are absent from malignant cells, and this difference in constitution should be demonstrable by immunological methods. Such an approach has been made by Weiler (1952), who compared the immunological properties of cytoplasmic particles from rat liver and from primary hepatoma induced by 4-dimethylaminoazobenzene (D.A.B.). He described an organ-specific antigen present in normal liver cells, but apparently absent from tumour. By means of the fluorescent antibody method he showed (1956a) that the livers of D.A.B.-treated rats developed islands of cells in which the antigen concentration was reduced in comparison with the surrounding parenchyma—that is, there was diminished staining of these islands in histological sections treated with specific anti-liver serum conjugated with fluorescein. The degree of antigen impoverishment varied with the total dose of carcinogen and the duration of the experiment. These findings indicated a correlation between loss of antigen and carcinogenic change. Similar observations were made in subsequent studies (1956b, 1956c) of stilboestrol-induced carcinoma in hamsters. The work, which has been recently reviewed (Weiler, 1959), has not, so far as we are aware, been confirmed by other workers, though an unsuccessful attempt to repeat it is reported by Hughes *et al.* (1957).

In the present investigation into the antigenic differences between normal tissues and tumours derived from them Weiler's findings in the D.A.B.-induced rat hepatoma have been corroborated. Similar results have also been obtained in preliminary studies of carcinoma in hamster kidney and of human skin tumours.

Methods

Liver Carcinoma in Rats

Production of Tumours.—The method was based on that of Griffin *et al.* (1948). Male albino rats (Tuck strain), weighing 200–250 g., were fed *ad lib.* for six months on a low-protein diet containing 0.06% 4-dimethylaminoazobenzene or for ten weeks on the low-protein diet containing 0.08% 3′-methyl-4-dimethylaminoazobenzene. When liver tumours became palpable the rats were killed by ether anaesthesia; thin blocks, each containing normal and tumour tissue, were "snap-frozen" in screw-cap bottles, pre-cooled in alcohol dry-ice freezing mixture, and stored at −20° C. Parallel blocks of tissue taken for conventional histological examination were fixed in formol-corrosive.

Preparation of Antigen.—Finely chopped fresh rat liver was suspended (10% w/v) in chilled 0.25 M sucrose buffered at *p*H 7.3 (0.1 M phosphate). The suspension was homogenized for four minutes at about 10,000 r.p.m. in an M.S.E. homogenizer. Further cellular disintegration, controlled by microscopical examination, was accomplished by means of the M.S.E.-Mullard ultrasonic disintegrator. A total of 90 seconds sonic treatment was given, resulting in breakdown of about 80% of cells with dispersal of cytoplasmic components; the majority of the nuclei remained intact. The cell components were separated as described by Weiler (1956a): 10 parts of the homogenate were layered on to one part of 10% sucrose solution, and centrifugation was carried out at 1,750 *g* for 7 minutes to remove tissue fragments and cell nuclei. The supernatant was then centrifuged at 9,000 *g* for 10 minutes to remove the mitochondrial sediment. Further centrifugation at 25,000 *g* for 90 minutes yielded cytoplasmic particles derived from the endoplasmic reticulum—that is, microsomal material, but presumably contaminated by fragments of cell membranes, nuclei, and mitochondria. This sediment was washed by resuspending in buffered sucrose followed by centrifugation, and the final sediment was snap-frozen in alcohol dry-ice freezing mixture and stored at −20° C. Weiler (1956a) showed that this final fraction provoked the best organ-specific antisera, and it was therefore used as antigen throughout the following experiments.

Production, Absorption, and Testing of Antiserum.—The antigen was suspended in buffered saline (0.01 M prosphate, *p*H 7.1) at a concentration of 3.75 mg. antigen nitrogen per ml., and administered to three 2.5-kg. cross-bred female rabbits in 0.5-ml. doses intravenously at two- or three-day intervals for 24 days; the total dose of antigen N given to each rabbit was 18–19 mg. The animals were bled six days after the last injection. One rabbit produced a good antiserum with a complement-fixing titre of 1/320, and this was used in subsequent experiments; the titres in the other two rabbits were only 1/80 and 1/40 respectively. Complement-fixation tests were carried out with serial doubling

dilutions of serum tested against 7.5γ antigen N; 3 M.H.D. of complement were used in the test and 2 M.H.D. in the controls. Fixation was carried out at 37° C. for 30 minutes, the haemolytic system added, and the results read after 30 minutes and 1 hour at 37° C. and after standing overnight at room temperature.

Immunological absorptions of the antiserum were carried out with acetone-dried tissue powders or with washed packed homogenates prepared from rat lung, kidney, liver, and hepatoma. The serum was shaken with powder (0.1 g. per ml.) or with homogenates (0.5 ml. per ml.) for 2 hours at room temperature; alternatively serum and homogenate were incubated at 37° C. for 30 minutes and allowed to stand overnight at 0° C. Serum was recovered, after absorption, by centrifugation at 10,000 *g* for 30 minutes. Successive absorptions were carried out in order to remove non-specific antibodies and leave only liver-specific antibody; this was removed by final absorption with liver powder or homogenate. The effect of successive absorptions was studied by (*a*) complement fixation; (*b*) gel diffusion by Mansi's (1958) modification of the Ouchterlony technique using 1.5 × 6 mm. wells 4 mm. apart; and (*c*) fluorescent antibody staining of tissue sections.

Staining with Fluorescent Antibody.—In order to obtain maximum staining sensitivity the "sandwich method" was adopted using labelled anti-rabbit-globulin serum prepared in a goat (G.A.R.G.), and the same general methods as described in a previous study (Nairn *et al.*, 1959). Direct staining was tried in preliminary experiments, but abandoned because the fluorescence with fully absorbed sera was too weak. Lissamine rhodamine B 200 (RB200) was used to prepare the fluorescent anti-rabbit-globulin conjugate (Chadwick *et al.*, 1958); it was absorbed with powdered activated charcoal (0.05 g. per ml. orginal serum), and then successively with rat liver powder, liver homogenate and lung homogenate, to eliminate non-specific staining. A few comparative experiments were also carried out with G.A.R.G. labelled with fluorescein isothiocyanate (Riggs *et al.*, 1958).

Frozen sections 5μ thick were cut from the snap-frozen blocks of rat liver in a low-temperature freezing cabinet at −18° to −20° C., and mounted on gelatin-coated slides. After drying for 1 hour at 0° C. in a current of air, the sections were treated with absolute ethanol at −8° C. for five minutes and again dried in the cold. They were stained on the same or the following day after storage at 0° C., by applying a drop of the anti-rat-liver rabbit serum for 60 minutes in a damp container. After rinsing and washing for 15 minutes in three changes of buffered saline (*p*H 7.1) the sections were treated with conjugated G.A.R.G. for 20 minutes, washed twice for 10 minutes, and mounted in buffered glycerol. Control sections from rat kidney were also studied. Fluorescence microscopy was carried out with the Reichert equipment modified for ultra-violet blue light as described previously (Nairn *et al.*, 1958). Absence of staining in tissues treated with (*a*) normal (pre-immunization) rabbit serum, or (*b*) immune serum fully neutralized by absorption with liver preparations, provided tests of specificity.

Renal Carcinoma in Hamsters

Production of Tumours.—Renal carcinomas were induced in male golden hamsters by unilateral nephrectomy and subcutaneous implantation of a 15-mg. pellet of hexoestrol (Horning, 1954). When a tumour became palpable the hamster was killed by ether anaesthesia and tissues were taken as described for the rat hepatoma.

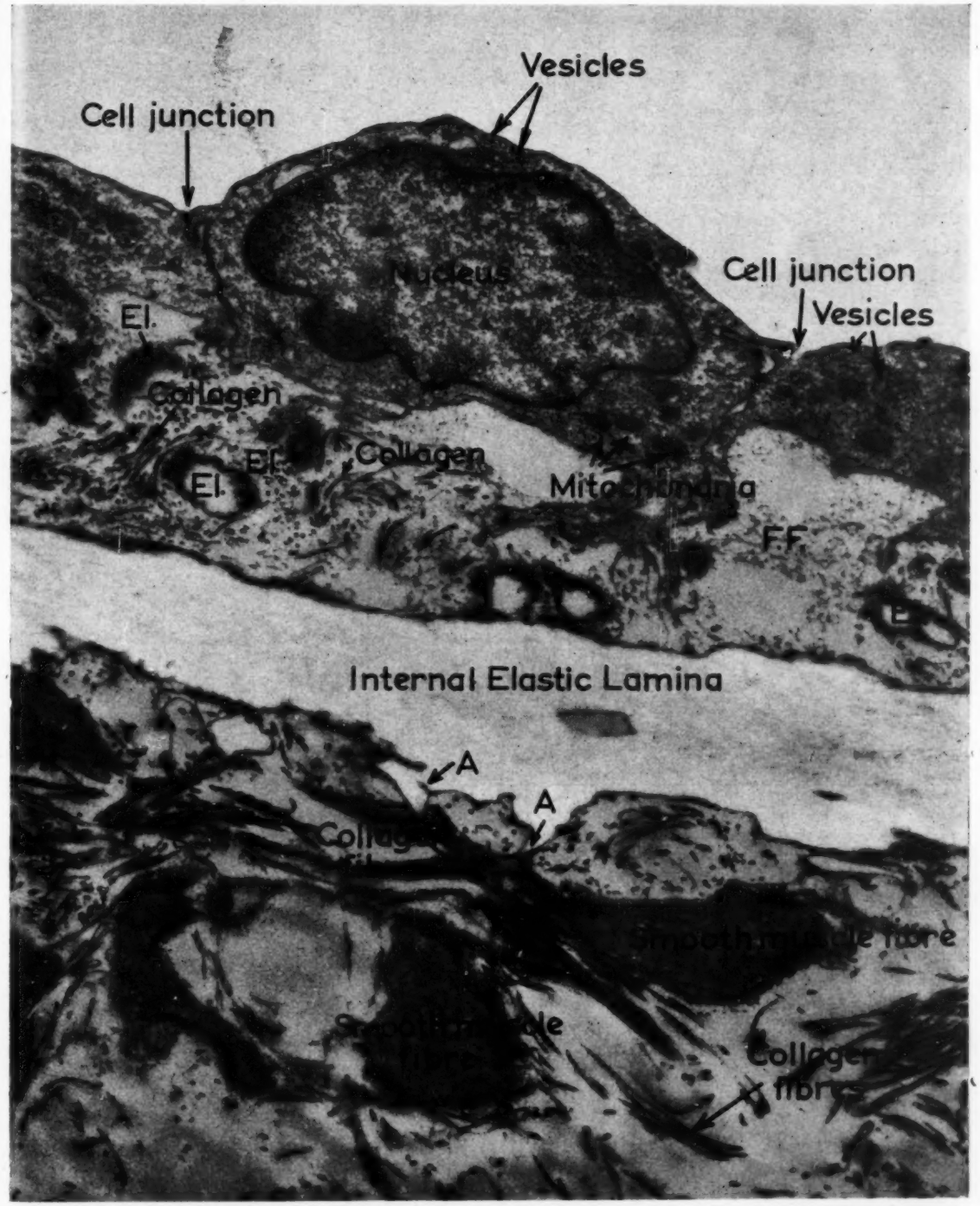
Preparation of Antigen.—Normal hamster-kidney homogenates were prepared in the same way as the rat-liver homogenates and centrifuged at 2,000 *g* for 8 minutes to remove tissue fragments and cell nuclei. The supernatant (0.8 mg. N per ml.), consisting of the remaining cytoplasmic particles and soluble components, was used without further refinement for the production and testing of immune sera.

Production, Absorption, and Testing of Antiserum.—Different immunization procedures, in several rabbits, were used for the production of antisera. The best serum happened to be produced by an animal which had been given intramuscularly 5 mg. antigen N in Freund's adjuvant including mycobacteria, followed six months later by two booster courses each of three daily injections of 0.8 mg. antigen N with an interval of six weeks between courses; the animal was bled five days after the last injection. This serum had a complement-fixing titre of 1/160 when tested against 16γ antigen N. It gave four lines against the antigen in gel-diffusion tests. Successive absorptions were carried out with packed sheep red cells to remove Forssman antibody, and with powders or homogenates prepared from hamster lung, liver, and renal carcinoma to remove non-specific antibodies and leave only kidney-specific antibody; this was removed by final absorptions with kidney powder and homogenate. As in the rat-liver studies, the effect of successive absorptions was analysed by complement fixation, gel diffusion, and fluorescent antibody staining. Sections of hamster kidney, renal carcinoma, and liver were stained by the same procedure as before; the conjugated G.A.R.G. was absorbed with activated charcoal, hamster liver powder, and homogenates of hamster lung and kidney.

Skin Tumours in Man

Representative blocks, including normal skin and tumour, were taken from a variety of human skin tumours, snap-frozen and stored at −20° C. Eighteen tumours were studied; 5 squamous carcinomas, 5 basal-cell carcinomas, 2 naevocarcinomas, 1 sweat-gland carcinoma, 2 papillomas, 2 benign naevi, and 1 benign sweat-gland tumour. Other blocks examined were from normal skin, keratotic lesions, 1 leucoplakia of lip, and 2 squamous carcinomas of oesophagus.

Preparation of Antigen.—Preliminary experiments had shown that skin is extremely resistant to disintegration by standard methods, and best results were obtained by the following procedure. Skin, taken with a Humby knife from the thigh of an adult man six hours after death, was finely chopped, suspended in buffered saline (0.01 M phosphate, *p*H 7.1), and treated in the homogenizer at 10,000 r.p.m. for 4 minutes. The resulting coarse homogenate was forced, frozen at −20° C., through a Hughes press (Hughes, 1951). The partially disintegrated skin was again homogenized at 10,000 r.p.m. and then given 3 minutes' sonic treatment. Though these procedures disrupted sufficient cells to provide the cytoplasmic components for preliminary studies, many intact cells and islands of squamous epithelium remained. Sucrose was added to the homogenate to make a 0.25 M solution, and tissue fragments and cell nuclei were removed by centrifugation



Intima of a coronary artery of a pig. The picture shows the substantial cellular nature of the endothelium. Small so-called pinocytotic vesicles and mitochondria are seen in the cytoplasm. In the subendothelial space are collagen, elastic (El), and other fine fibres (FF). The internal elastic lamina is clearly defined, and deep to this is the media. At A are attachments of smooth muscle cells of the media to the internal elastic lamina. The artery was fixed in a contracted state. It is probable that in life the endothelium would be flatter and nearer to the internal elastic lamina. (Electronmicrograph. ×16,500.)

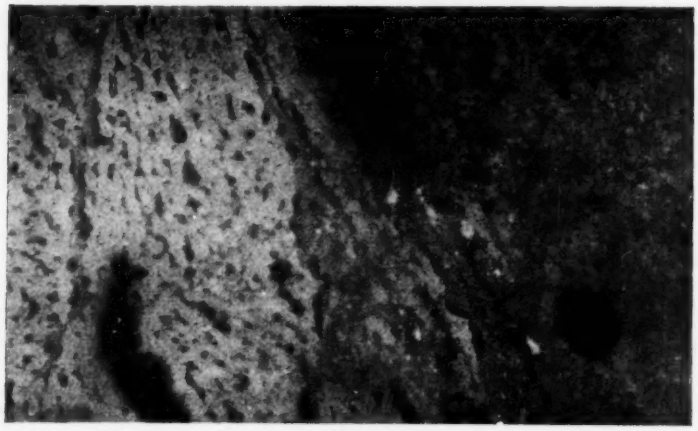


FIG. 1

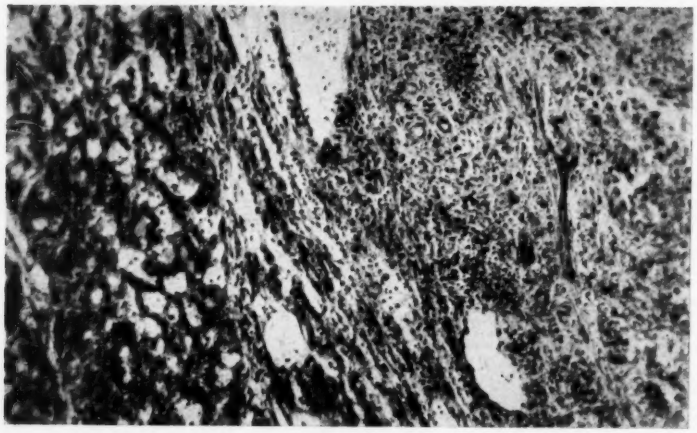


FIG. 2

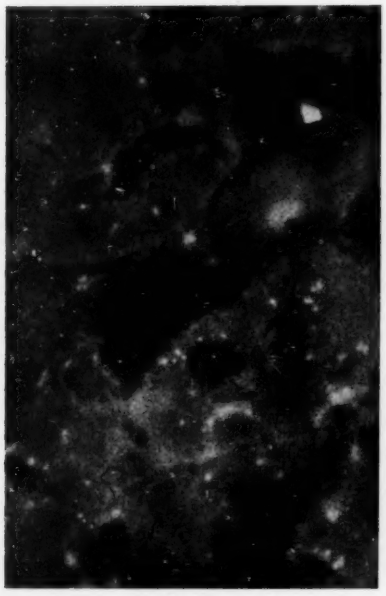


FIG. 3

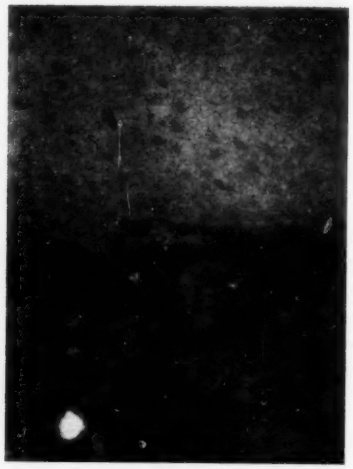


FIG. 4

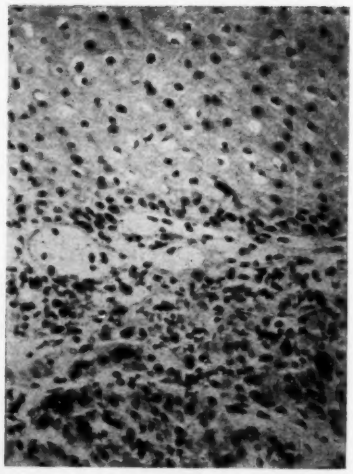


FIG. 5

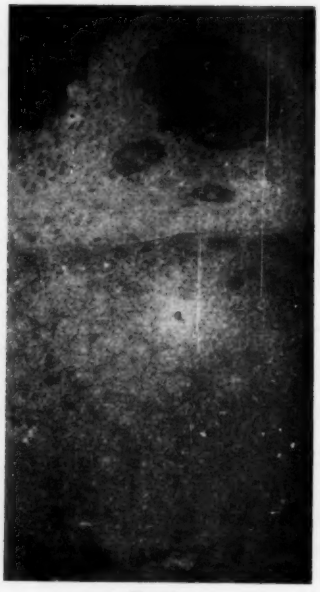


FIG. 6

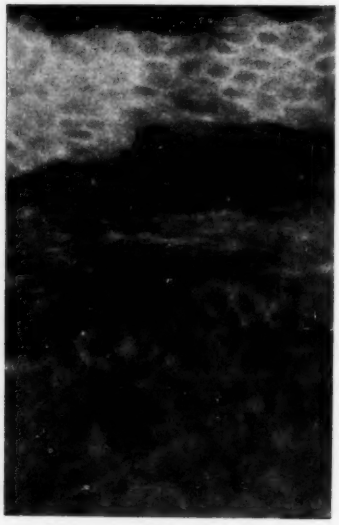


FIG. 7

at 2,000 *g* for 8 minutes; the supernatant (0.4 mg. N per ml.) was used as skin antigen without further refinement.

Production, Absorption, and Testing of Antiserum.—There was only enough antigen to immunize one rabbit, which was given initially 4 mg. antigen N in Freund's adjuvant, including mycobacteria, intramuscularly, and six weeks later a booster course of three daily intraperitoneal injections of 0.8 mg. antigen N. At further intervals of four weeks the booster course was repeated twice; the animal was bled five days after the last injection. There was insufficient antigen for complement-fixation tests, and the serum was therefore studied by gel diffusion and fluorescent-antibody staining. Sections of human skin, skin tumours, liver, and kidney were studied; the conjugated G.A.R.G. was absorbed with activated charcoal, human liver powder, and homogenates of human lung and skin.

Results

Liver Carcinoma in Rats

The effects of the various immunological absorptions on the anti-rat-liver serum are summarized in Table I. A fall in complement-fixing titre was often observed when tests were repeated, due, we believe, to some impairment of the antigen during storage, freezing, and thawing; where this has occurred a range of titres is given. Despite these variations, there was progressive loss of titre with successive absorptions: after absorbing first with lung homogenate, secondly with kidney powder, and thirdly with kidney homogenate, the titre fell from 1/320–1/160 to 1/20–1/5; when tumour homogenate instead of kidney homogenate was used for the third absorption the titre fell to 1/5–1/2.5; there was complete loss of titre when liver homogenate was used for the third absorption. The same results were obtained in a few parallel experiments when, instead of homogenates, tumour powder and liver powder respectively were used for third absorptions.

A similar progressive loss of antibody components was observed when sera from successive absorptions were tested against the liver antigen by gel diffusion. The production of specific precipitin lines by this technique indicates that the antigen suspension was partially soluble. Unabsorbed serum gave three specific lines, and serum absorbed with lung homogenate gave two lines; after absorption of this serum with kidney powder and homogenate two lines (one faint) could still be obtained. When tumour homogenate was used for the third absorption the serum gave a single line; there was no line when liver homogenate was used for this absorption. Normal serum, unabsorbed or absorbed, gave no lines.

The fluorescent-staining reactions of sections of rat liver and tumour and of normal rat kidney are also shown in Table I. Twenty tumour blocks obtained from six rats were studied; they included hepatomas, cholangiomas, and mixed types, and showed a wide range of differentiation and anaplasia. The table presents a composite picture of the staining obtained by applying the RB200-conjugated G.A.R.G. after treatment of the sections with the normal and immune sera with and without absorptions. The unabsorbed anti-liver serum gave strong diffuse staining of liver parenchyma and of tumour, but less staining of normal rat kidney. After a single absorption with lung homogenate the staining was more clearly defined, and obviously more intense in liver than in tumour and least intense in kidney. Further absorptions with kidney powder and homogenate abolished kidney staining by the serum, but staining could still be obtained in liver and to a minor extent in tumour. When tumour homogenate was used for the third absorption of the serum, staining was diminished in the liver and virtually absent in the tumour; there was no staining when liver homogenate was used for the third absorption. Normal serum gave slight, diffuse, non-specific staining equally in liver, tumour, and kidney, and no staining after absorption with rat-tissue preparations. Some of the liver sections contained hyperplastic, possibly pre-neoplastic, nodules of liver cells, which were stained by the antiserum with an intensity somewhere between the staining of normal liver and of carcinoma.

The localization of specific staining by highly absorbed sera in the liver parenchyma was mainly in the cell membrane and in the perinuclear zone, with faintly staining granules elsewhere in the cytoplasm; occasionally the cytoplasmic staining appeared to be diffuse rather than granular (Special Plate, Figs. 1 and 2). Staining of tumour cells by less fully absorbed sera was more diffuse, though the perinuclear component could usually be distinguished. Incompletely absorbed sera gave some staining of connective tissue and conspicuous staining of vascular lining in liver, tumour, and kidney; staining of renal tubular epithelium was minimal even with unabsorbed serum.

DESCRIPTION OF SPECIAL PLATE

All except Figs. 2 and 5 are fluorescence photomicrographs of frozen sections stained by "sandwich method" with RB200-conjugated goat anti-rabbit globulin after treatment with absorbed anti-organ rabbit sera. The large bright spot in Figs. 3, 4, and 6 is an artifact used as an aid to focusing.

FIG. 1.—Rat-liver section treated with anti-rat-liver serum which had been absorbed successively with rat lung homogenate, kidney powder, and kidney homogenate. Fluorescent staining is brighter in the normal parenchyma, to the left, than in the carcinoma, to the right. The diffuse appearance of the fluorescence is due in part to limitations of the photomicrography. (×120.)

FIG. 2.—Parallel section to Fig. 1 fixed in formol-acetate and stained with haematoxylin and eosin. Between the normal and carcinoma there is a necrotic zone infiltrated with leucocytes. (×120.)

FIG. 3.—Normal hamster-kidney section treated with anti-hamster-kidney serum which had been absorbed successively with hamster-lung homogenate, sheep red cells, hamster-renal-tumour powder and homogenate. There is fluorescent staining of cell membrane of renal tubular cells, particularly of the brush border of a proximal convoluted tubule, top left; crescentic perinuclear staining and a few fluorescent cytoplasmic particles can also be seen. (×830.)

FIG. 4.—Human squamous carcinoma section treated with anti-human-skin serum which had been absorbed successively with human lung homogenate, liver powder, and liver homogenate. Normal epidermis, above, has stained more brightly than tumour, below. (×180.)

FIG. 5.—Same field as Fig. 4 after staining with haematoxylin and eosin, showing normal epidermis with underlying poorly differentiated carcinoma. (×180.)

FIG. 6.—Human naevocarcinoma treated with same serum as in Fig. 4, showing the same contrast between normal epidermis and underlying tumour; aggregates of dimly staining naevocarcinoma cells can also be seen in transected dermal papillae. (×120.)

FIG. 7.—Human basal-cell carcinoma section treated with same serum as in Figs. 4 and 6. Bright fluorescent staining of cell membrane is well shown in normal epidermis, above, and contrasts with dimmer staining of the tumour cells, below. (×550.)

The histological findings were similar in the few experiments in which G.A.R.G. conjugated with fluorescein was used, but, owing to lack of colour contrast with tissue autofluorescence, definition was poorer and localization to the cell membranes less conspicuous. Photomicrographs of such preparations may be misleading, since the autofluorescence of normal liver is usually brighter than that of carcinoma, and thus augments the difference in fluorescence between the two tissues when they are stained with a fluorescein conjugate.

The three methods of immunological analysis show parallel changes in the anti-rat-liver serum after successive absorptions. The results, in particular the gel-diffusion analysis, suggest that the antigen contains at least three distinct components. Two of these are present in tissue other than liver and are therefore not organ-specific. The third component appears to be organ-specific; it may or may not be exclusive to liver, but is undoubtedly present in much higher concentration in the liver than in the other tissues used for the serum absorptions. The precipitin line produced by the tumour-absorbed antiserum could still be obtained after reabsorption of the serum with tumour homogenate. Thus it would seem that the liver-specific component of the antigen is either absent altogether from the liver tumour or at most present in very small amount.

Renal Carcinoma in Hamsters

The reactions between hamster tissues and the anti-hamster-kidney serum after successive absorptions showed the same general pattern (Table II) as in the rat-liver experiments. Absorption of the antiserum with hamster-lung homogenate to remove species-specific antibodies to hamster tissue, in particular reticulin, and with sheep red cells to remove Forssman antibody, resulted in a fall in the complement-fixation titre from 1/160 to 1/10. The titre remained at 1/10 after two further absorptions with liver powder and homogenate or with renal tumour powder and homogenate. Kidney powder and homogenate caused a reduction in titre, possibly complete loss, but this could not be measured because we were unable to overcome the anticomplementary activity of the serum after these absorptions.

Parallel changes occurred in the gel-diffusion tests: serum before absorption gave four lines with the kidney antigen and two lines (one faint) after absorptions with lung homogenate and sheep red cells. The strong line

TABLE I.—*Reactions of Unabsorbed and Absorbed Anti-rat-liver Rabbit Serum*

Absorptions with Rat-tissue Preparations:	Anti-rat-liver Serum					Normal (Pre-immunization) Serum	
	Nil	Lung Homog.	Lung Homog. + Kidney Powder + Kidney Homog.	Lung Homog. + Kidney Powder + Tumour Homog.	Lung Homog. + Kidney Powder + Liver Homog.	Nil	Lung Homog. + Kidney Powder + Kidney Homog.
Complement-fixation titre against 7·5 γ antigen N*	1/320–1/160	1/80	1/20–1/5	1/5–1/2·5	0	0	...
Gel-diffusion lines at 48 hours against antigen (3·75 mg. N per ml.)	3	2	2† (1 faint)	1†	0	0	0
Staining of rat tissues with fluorescent antibody ‡							
Liver—normal	++++	+++	+(+)	+	–	(+)§	–
Liver—tumour	++++	++	(+)	(–)	–	(+)§	–
Kidney—normal	+++	+	(–)	(–)	–	(+)§	–

(+) = Minor staining. (–) = Minimal patchy staining sometimes seen. * Range given where repeated tests differed in titre. † One line still obtained after further absorption with kidney or tumour homogenate. ‡ Composite picture from all experiments. § Diffuse non-specific staining.

TABLE II.—*Reactions of Unabsorbed and Absorbed Anti-hamster-kidney Rabbit Serum*

Absorptions with Hamster-tissue Preparations:	Anti-hamster-kidney Serum					Normal (Pre-immunization) Serum	
	Nil	Lung Homog. + Sheep Red Cells	Lung Homog. + Sheep Red Cells + Liver Powder and Homog.	Lung Homog. + Sheep Red Cells + Tumour Powder and Homog.	Lung Homog. + Sheep Red Cells + Kidney Powder and Homog.	Nil	Lung Homog. + Liver Powder
Complement-fixation titre against 16 γ antigen N	1/160–1/80	1/10	1/10	1/10	Anticomplementary < 1/10	0	...
Gel-diffusion lines at 48 hours against antigen (0·8 mg. N per ml.)	4	2 (1 faint)	1	1	0	0	0
Staining of hamster tissues with fluorescent antibody:							
Kidney—normal	++++	+++	+++	+++	(+)	(+)	–
Kidney—tumour	++++	+++	+(+)	+	(+)	+	(+)
Liver—normal	++	+(+)	(–)	(–)	(–)	(+)	–

TABLE III.—*Reactions of Unabsorbed and Absorbed Anti-human-skin Rabbit Serum*

Absorptions with Human-tissue Preparations:	Anti-human-skin Serum				Normal (Pre-immunization) Serum	
	Nil	Lung Homog. + Liver Powder	Lung Homog. + Liver Powder + Liver Homog.*	Lung Homog. + Liver Powder + Skin Homog.*	Nil	Lung Homog. + Liver Powder + Liver Homog.
Gel-diffusion line at 48 hours against antigen (2 mg. N per ml.)	3	1	1	1 faint†	0	0
Staining of human tissues with fluorescent antibody:						
Skin—normal, hyperplastic, and papilloma	+++	+++	++	(–)	(+)	–
Skin—carcinoma	+++	++	+	(–)	(+)	–
Kidney and liver—normal	++	+	–	–	(+)	–

* The results were the same whether the serum was absorbed once or twice with these homogenates. † Abolished by treatment with freeze-dried soluble material from skin homogenates.

could still be obtained after two further absorptions of the serum with liver or tumour preparations, but there were no lines when kidney preparations were used for these absorptions. Normal serum gave no lines. The results suggest that the antigen component responsible for the single line against the highly absorbed serum is kidney-specific and is absent from the tumour tissue.

This conclusion is supported by the fluorescent-staining reactions. Four tumour blocks from two renal carcinomas were studied; the staining was compared with that of the adjacent normal kidney and with normal kidney and liver blocks from other hamsters. The reduction of staining in kidney, tumour, and liver, after successive absorptions of the antiserum, followed the same pattern as the other immunological tests. The difference in staining between the three tissues also fits with the rest of the findings: with unabsorbed serum staining was intense and diffuse in kidney and tumour, and less intense in liver; after absorption with lung and sheep red cells the serum gave brilliant, clearly defined staining of kidney and tumour and less staining of liver. Further absorptions by liver or tumour preparations did not diminish the staining of kidney, though staining was reduced in tumour and virtually abolished in liver; there was little or no staining after the absorptions with kidney preparations. The normal sera gave unusually bright, diffuse staining of tumour, presumably a non-specific physical effect. The specific staining of kidney produced by the highly absorbed sera was located mainly in the tubular epithelial cells in cell membrane, the perinuclear zone, and in a few cytoplasmic granules (Special Plate, Fig. 3); there was also some glomerular staining. Staining of tumour by the highly absorbed sera was confined to the cell membrane. With incompletely absorbed sera there was more granular cytoplasmic staining, less prominent in tumour than in normal kidney tubules. Unabsorbed sera also gave staining of vascular lining and connective tissue in kidney, tumour, and liver.

Skin Tumours in Man

The results of fluorescent-antibody staining of human tumours (Table III) were strikingly similar to those obtained with the animal tumours. The unabsorbed serum gave strong diffuse staining of normal skin and all skin tumours, and less staining of control sections of normal human kidney and liver. After absorption of the serum with lung homogenate and liver powder the staining of normal skin was just as bright, more clearly defined, and limited to the epidermis; there was much less staining of the control sections. After further absorption with liver homogenate the difference was even more obvious. Thus it was clear that this highly absorbed serum had selective affinity for skin; the same affinity was shown for benign tumours of skin—that is, there was no difference between the staining of these tumours and of the adjacent normal epithelium. Malignant skin tumours, however, stained less intensely than normal epithelium (Special Plate, Figs. 4–7). All staining was virtually abolished when skin homogenates were used for the final absorption. For effective absorption the skin homogenates required the same drastic methods of preparation as previously employed for the production of skin antigen; less disrupted preparations were ineffective.

The specific staining of epidermis by the highly absorbed sera was largely confined to the cell membranes, and was more intense in the basal-cell than the prickle-cell layer; some cytoplasmic granular staining was also present. The same pattern and degree of staining were observed in hyperplastic papillae of the keratotic and leukoplakic lesions and in the papillomas. Staining was diminished in 12 of the 13 carcinomas (a naevocarcinoma was the only exception); it was confined to cell membrane, and contrasted sharply with the bright staining of the adjacent normal epidermis. The extra fluorescent staining seen in the basal-cell layer of normal epidermis had no counterpart in the peripheral-cell layer of tumour masses in the dermis. The oesophageal carcinoma also showed reduced staining in the islands of cancer cells when compared with the adjacent normal and hyperplastic epithelium.

The changes observed when the sera from successive absorptions were tested by gel diffusion were less systematic. In order to obtain satisfactory lines the antigen was concentrated to 2 mg. N per ml.; it gave three lines against the unabsorbed serum, and one sharp line after absorption of the serum with lung homogenate and liver powder. A sharp line could still be obtained after further absorption with liver homogenate, but only a faint line was produced when skin homogenate was used for the absorption. This faint line could also be demonstrated after additional absorption with sheep red cells or human red cells (Group A, B, or O), but not after treatment with freeze-dried soluble material from skin homogenates. Failure to absorb the serum completely with washed skin homogenates is perhaps explained by the difficulty of making such preparations satisfactorily, and this problem was never entirely overcome. Various means, such as the preparation of squamous-epithelial-cell homogenates from microtome sections of oesophageal mucosa, were only partially effective. Scarcity of antiserum precluded further attempts to solve the problem, and we were unable to study parallel absorptions by normal skin and skin-tumour preparations.

The fluorescent-staining experiments suggest that the antiserum contains specific antibody to antigen present in normal skin epidermis and in benign skin tumours; in malignant tumours the amount of antigen is reduced. This antigen may be responsible for the single precipitin line obtained with the absorbed sera, but the evidence is not conclusive.

Discussion

These findings suggest that mammalian cells contain organ-specific antigen or antigens which are lost or depleted when the cells become malignant, whether the malignancy is chemically induced or spontaneous. The results are most clear-cut in the rat-liver study, possibly because the antigen was less crude than in the other investigations. Nevertheless, all three studies gave consistent results, especially with the fluorescent-antibody method. In normal rat liver, hamster kidney, and human epidermis staining was strongest in the cell membranes. This localization is not described in Weiler's studies; he used fluorescein-labelled antibody for staining, and cell-membrane staining is less conspicuous with this method than with RB200 labelling. Affinity of the specific antiserum for cell membrane is not unexpected; our antigens contained endoplasmic reticulum, which may have morphological continuity with cell membrane (Robertson, 1959), and hence there might well be antigenic components common to both structures. Cytoplasmic staining, seen best in the rat liver, was less obvious in hamster kidney and least in human skin. This variation is not necessarily due to fundamental differences in the tissues themselves, but

may merely reflect technical differences in the production of the antigens and hence the antisera.

Apart from the visual information from fluorescent staining, the principal evidence for the organ-specificity of the rat-liver and hamster-kidney antisera is the failure to abolish immunological activity except by absorptions with rat-liver or hamster-kidney preparations respectively. The persistence of complement-fixing activity and the production of a single precipitin line against the antigen, by sera repeatedly absorbed with other tissues, support this view. The general pattern of results with the human-skin antiserum follows the animal studies so closely that it seems reasonable to regard the serum as organ-specific. The evidence for antigen depletion in the tumours compared with the normal tissues is provided by their differential staining with labelled antiserum and their differential antibody-neutralizing properties. The depletion may be absolute in the experimental carcinomas, but appeared to be only partial in human skin cancer. Hiramoto and Pressman (1957), in a brief report of fluorescent-staining reactions by an anti-human-skin serum, mention selective staining of skin tumours by the serum, but not differential staining.

There is close correspondence between our results and those of Weiler, and the failure of Hughes *et al.* to produce a rat-liver-specific antiserum is difficult to understand. These authors infer that the differential staining of normal tissue and tumour demonstrated by Weiler may have been a non-specific reaction, but this interpretation ignores the careful controls in Weiler's experiments; similar controls have also been used in the present studies. We (Nairn *et al.*, 1960) have examined the kind of non-specific staining described by Hughes *et al.*, and conclude that it is different in kind and degree from that produced by organ-specific antisera.

What bearing has the loss of organ-specific antigen on carcinogenesis? The protein-deletion theory (Miller and Miller, 1952) postulates that the binding of carcinogens to growth-controlling cell proteins leads to inactivation of these proteins, which thus fail to be replicated in subsequent cell divisions. The daughter cells are neoplastic because they lack the growth-control factor. Vogt (1958, 1960) has shown that the organ-specific antigen in rat liver is found in the membranes of the endoplasmic reticulum, and he suggests that degradation of these membranes in the course of carcinogenesis contributes to the uncontrolled activity of the cancer cell. The site and the organ-specificity of the antigen loss may, however, have other implications. Green (1959) has suggested that growth of normal cells is controlled immunologically by virtue of the presence of specific lipoproteins; absence of such "self markers" permits neoplastic behaviour. As it is reasonable to suppose that the organism may identify its cells by their surface structure, then our observation that the cell membrane is an important site of organ-specific antigen may be significant.

Summary

An alteration in cell constituents associated with malignant change has been investigated by immunological methods. Three types of normal and tumour tissue were compared: rat liver and hepatoma (induced by aminoazo-dye feeding); hamster kidney and renal carcinoma (induced by oestrogen implant); human skin and various skin tumours (occurring spontaneously in man). In each study antigen was prepared from homogenized normal tissue, which was centrifuged to remove tissue fragments and cell nuclei. For the hamster-kidney and human-skin experiments rabbits were immunized with the crude supernatants; for the rat-liver study the homogenate was further refined so that the antigen used for immunization consisted mainly of cytoplasmic particles derived from the endoplasmic reticulum—that is, microsomal material.

The rabbit antisera were tested against the corresponding normal and tumour tissues by three methods, using appropriate tissue preparations to absorb and remove non-organ-specific antibodies: (1) complement fixation; (2) gel-diffusion analysis; and (3) fluorescent staining by the "sandwich" technique. Control studies were carried out with normal (pre-immunization) serum and immune serum specifically neutralized by absorption with preparations of the homologous organ. In the rat-liver and hamster-kidney experiments all three methods indicate the presence of an organ-specific antigen in liver and kidney respectively; the antigens are either absent from, or at most present in very small amount in, the corresponding tumour. In the malignant tumours of skin a partial depletion of specific antigen was demonstrated; technical difficulties in preparing skin and skin-tumour homogenates for control absorptions prevented more complete analysis. The fluorescent-antibody studies suggest that the specific antigen is localized in the cell membrane and in the perinuclear zone, with some faintly staining granules elsewhere in the cytoplasm.

One interpretation of these findings is that the lack of organ-specific antigen may indicate absence of a particular growth-controlling factor from malignant cells. The localization of the antigen to normal cell membrane may have special significance and be related to surface identification of the cell. Controlled normal growth might require such a "self-marker," and its absence would lead to uncontrolled malignant growth.

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DIFFERENCES IN STAINING OF NORMAL AND MALIGNANT CELLS BY NON-IMMUNE FLUORESCENT PROTEIN CONJUGATES

BY

R. C. NAIRN, M.D., Ph.D.

H. G. RICHMOND, M.D.

AND

J. E. FOTHERGILL, Ph.D., B.Sc.

From the Departments of Pathology and Biological Chemistry, University of Aberdeen

Differential staining of normal and malignant tissue by normal serum globulin labelled with fluorescein was described in 1957 by Hughes, Louis, Dineen, and Spector. In the course of an attempt to repeat Weiler's (1956) fluorescent antibody studies of rat hepatoma, they found that labelled non-immune rabbit globulin (N.R.G.) stained normal liver but not tumour, and that the fluorescent staining appeared to be similar to that obtained by Weiler with labelled organ-specific antiserum. The staining reaction with non-immune serum has been observed in human and experimental material and has been produced with different serum-protein fractions from several animal species (literature quoted by King, Hughes, and Louis, 1958). It has been suggested that the reaction might provide a simple histological test of malignancy.

In the present study the staining method with non-immune conjugates has been applied to a variety of tumours, human and experimental, and our results do not show a uniform pattern. Normal tissue stained more brightly than tumour in some cases, particularly in colonic carcinoma, but in others there was no differential staining and occasionally the normal tissue stained less brightly than tumour. In a few experiments our histological findings have been compared with the results of centrifugation and electrophoresis of mixtures of conjugated N.R.G. with homogenates of normal and tumour tissue. This comparison suggests that the soluble rather than the particulate components of the cells are concerned in the non-specific staining.

Methods

Human tumours were collected mainly from operation specimens immediately after resection, and occasionally from necropsies when death had occurred less than eight hours previously. Blocks containing both tumour and normal tissue were "snap-frozen" in screw-cap bottles pre-cooled in alcohol-dry ice mixture, or were frozen in a tube of isopentane immersed in the freezing mixture. The following types of tumour were studied:—*Skin:* squamous carcinoma; basal-cell carcinoma; naevocarcinoma; sweat-gland carcinoma; papilloma; benign naevus; benign sweat-gland tumour. *Oesophagus:* squamous carcinoma. *Stomach:* spheroidal-cell carcinoma; adenocarcinoma. *Colon:* adenocarcinoma; benign polyp. *Kidney:* hypernephroma. *Breast:* carcinoma; fibroadenoma. *Pancreas:* carcinoma. *Salivary gland:* mixed tumour. Some hyperplastic, possibly preneoplastic, conditions were also examined—namely, cystic epithelial hyperplasia of breast, and keratotic and leucoplakic lesions of skin.

Animal tumours from rat liver and hamster kidney, as in the preceding paper (Nairn, Richmond, McEntegart, and Fothergill, 1960), were also used in the present investigation.

Histological Studies

For section cutting and staining, the same general methods as in the preceding paper were used. Frozen sections, 5 μ thick, mounted and dried, were treated with absolute ethanol at $-20°$ C. for 15 minutes and again dried at 0° C. They were stained for 10 minutes with N.R.G. conjugated with lissamine rhodamine B 200 (RB200); after rinsing and washing for 10 minutes in two changes of buffered saline (0.01 M phosphate, *p*H 7.1) they were mounted in buffered glycerol and examined by fluorescence microscopy. In order to compare the results with those of King *et al.* (1958), a parallel series of experiments was carried out using the same methods (Hughes, 1958) with fluorescein conjugates, prepared from fluorescein isocyanate derived from isomer I aminofluorescein (Coons and Kaplan, 1950). The conjugates were extracted with ethyl acetate (Dineen and Ada, 1957), a method which leaves a substantial proportion of unreacted fluorescent material (U.F.M.) adsorbed on the protein.

The possible influence of such U.F.M. on staining was studied in a further series of experiments using fluorescein conjugates treated with activated charcoal, which removes the U.F.M. almost completely (Chadwick and Nairn, 1960). Other staining experiments were carried out with an aqueous solution of U.F.M. prepared by a mock conjugation procedure in which fluorescein isocyanate was mixed with carbonate-buffered saline (*p*H 9) but without the addition of serum protein. This mixture was stirred overnight, and then diluted with a large volume of phosphate-buffered saline (*p*H 7.1) to make a solution of the same fluorescence intensity as the fluorescein-conjugated N.R.G. which had been extracted with ethyl acetate. The nature and staining properties of this U.F.M. solution are discussed elsewhere (Chadwick and Nairn, 1960). For comparison with the fluorescent staining, sections treated with brilliant cresyl blue, haematoxylin and eosin, and methyl-green-pyronin were also examined.

Centrifugation and Electrophoretic Studies of Tissue Homogenates

Normal and carcinoma tissue from human colon (one post-mortem and five surgical specimens), human kidney (one post-mortem and one surgical specimen), and rat liver (one specimen) were homogenized in 3 vols. buffered saline (*p*H 7.1) containing penicillin and streptomycin (500 units/ml. of each) by means of an M.S.E. homogenizer at 10,000 r.p.m. for four minutes. The homogenates were diluted to 10% (w/v) and further cellular disintegration was accomplished by means of the M.S.E.–Mullard ultrasonic disintegrator. Tissue homogenates and RB200-conjugated N.R.G. were mixed in the ratio 30 parts tissue protein nitrogen to 1 part N.R.G. nitrogen and allowed to stand at 0° C. for 30 minutes before centrifuging at 105,000 *g* for 45 minutes; appropriate blanks were run in parallel. In early experiments the medium included sucrose (0.25 M), but this had no effect on the results and was omitted subsequently.

Spectrophotometric optical density measurements at 565 mμ were carried out on the supernatants to determine if any of the conjugate had been absorbed by the subcellular particles. These supernatants, presumably mainly protein in solution, were not fluor-

escent enough for satisfactory electrophoretic study, and therefore they were concentrated by evaporation, dialysed against 0.2 M borate buffer at *p*H 8.6 (Adjutantis, 1954), and adjusted to a protein concentration of 10 mg./ml.; more RB200-conjugated N.R.G. was added to make mixtures of equal parts of N.R.G. and tissue protein. Electrophoresis was carried out in the borate buffer, using an E.E.L. apparatus; 20 μl. of each fluorescent mixture was applied to a 34 by 5 cm. strip of Whatman No. 1 filter paper and a current of 1.5 mA passed for 16 hours. Dried filter-paper strips were examined under ultra-violet light, and a visual estimate was made of the intensity of fluorescence on the starting-line. This was compared with that of a control run with RB200-conjugated N.R.G. alone, most of which remains on the starting-line at *p*H 8.6. The difference gave an indication in each of the fluorescent mixtures, of the proportion of RB200-conjugated N.R.G. which had migrated in association with the tissue proteins.

Results

In the accompanying Table the staining with RB200-conjugated N.R.G. of 65 human and 8 animal tumours is compared with that of the adjacent normal tissues.

Comparison of Fluorescent Staining of Normal and Tumour Tissue by Normal Rabbit Globulin Conjugates

	Comparative Staining		
	Normal >Tumour	Normal =Tumour	Normal <Tumour
Human carcinomas:			
Skin (18)	7	11	
Oesophagus (2)	1	1	
Stomach (6)	3	2+1*	
Colon (14)	12	1+1*	
Kidney (5)		1+2*	2*
Breast (6)	2	3	1
Pancreas (1)	1		
Animal carcinomas:			
Rat liver (6)	1	5	
Hamster kidney (2)	1		1
Human benign tumours:			
Skin (8)	1	7	
Colon (3)		2+1*	
Breast (1)			1
Salivary gland (1)			1
Total (73)	29	38	6

* Necropsy material.

Only the human colon carcinomas showed a definite trend of brighter staining in the normal mucosa compared with tumour (12 out of 14 cases); two cases showed equal staining, but one of these was necropsy material. Almost the opposite result was obtained in the five renal carcinomas, four of which were necropsy material: two showed brighter staining of tumour and three equal staining of tumour and normal. One other human carcinoma, from the breast, showed brighter staining of tumour. The carcinomas of the skin, oesophagus, stomach, and pancreas showed equal or less staining when compared with the normal tissues. Five rat hepatomas showed equal staining with the normal rat liver and one showed diminished staining. One hamster kidney tumour stained less brightly and the other more brightly than the normal kidney. One of 13 benign tumours stained less, 10 equally, and 2 more brightly than the corresponding normal tissue. The hyperplastic lesions (one case of cystic epithelial hyperplasia of breast, one leucoplakia of lip, and three keratoses of skin) showed equal staining in normal and abnormal tissue.

Many other tumours and hyperplastic lesions were examined, but staining comparisons could not be made because the tissue blocks did not include identifiable samples of both normal and abnormal tissue. This sampling problem was particularly troublesome with breast tumours, in which it was always difficult to include representative normal acini in the same block as tumour. For all practical purposes our results were the same whether sections were taken immediately from tissue blocks frozen in isopentane or from stored snap-frozen material, and whether staining was carried out with RB200-conjugated N.R.G. or with fluorescein conjugates. Assessment of the degree of staining by fluorescein conjugates required the examination of parallel unstained sections to allow for the effect of autofluorescence; this is usually brighter in normal than in carcinoma tissue, partly because of a greater concentration of non-fluorescent nuclear material in tumour.

These control studies are of particular importance since colour contrast is poor between the green of fluorescein conjugates and blue-green of autofluorescence, and the staining was often dim and diffuse. The orange fluorescent staining with RB200-conjugated N.R.G. was easier to assess because of better contrast with autofluorescence. Another difficulty in the interpretation of staining of the carcinomas was the frequent occurrence of areas of necrosis which not only had different autofluorescence from the rest of the tissue but showed inconsistent staining reactions: fluorescent staining of necrotic areas was usually weak, but occasionally it was intense.

Staining by fluorescein conjugates extracted with ethyl acetate was brighter than with charcoal-treated conjugates, presumably because of a contribution from U.F.M. adsorbed on the serum globulin. The influence of this U.F.M., which probably comprises aminofluorescein and another fluorescent product of hydrolysis of fluorescein isocyanate, was studied in parallel experiments. Staining with aqueous U.F.M. solution was more brilliant than with conjugated N.R.G.: its distribution was more often equal in the tumour and normal tissues (in 46 of the 73 tumours); six carcinomas (three skin, one stomach, one colon, and one breast) gave greater staining in the normal tissue, though staining with N.R.G. conjugates was equal in tumour and normal.

The intracellular distribution of staining by the fluorescent conjugates was usually diffuse in the cytoplasm except in normal colonic mucosa celis, which showed sharp peripheral staining and clearly outlined non-fluorescent vacuoles. Some degree of staining was seen in all tumours and corresponding normal tissues; this is contrary to the experience of King *et al.*, who record no staining in malignant tumours. In all tissues, staining was commonly dim, and differences between tumour and normal were often so small that time and histological judgment were required for any distinction to be made. No correlation was observed between the intensity or distribution of the fluorescent staining and the ribonucleic acid content of the cells as indicated by the pyronine reaction. There was, however, close correlation with the acidophilic—for example, eosinophilic—cytoplasmic staining; basophilic cells showed less affinity for the fluorescent conjugates. The histological findings suggest, therefore, that this non-specific fluorescent staining of normal tissue and tumour by N.R.G. conjugates is a property of cytoplasm similar to that demonstrated by conventional staining methods. This view is supported by the staining results with the

U.F.M. solution, which, from its probable chemical composition, would be expected to behave like eosin.

Studies of Tissue Homogenates.—In the nine experiments comparing the affinities of RB200-conjugated N.R.G. for normal and tumour homogenates, the optical densities of the supernatants after centrifugation showed no loss of conjugate—that is, there was no apparent absorption of conjugate by the sedimented material. The method is sensitive enough to detect a 10% absorption of conjugate which would represent 1 part of conjugate to 200 parts of sediment. Visual comparison of the electrophoretic strips from the normal and tumour supernatants showed greater affinity of the conjugate for normal than for tumour protein in four samples of human colon carcinoma—that is, there was less fluorescence on the starting-line of the normal sample. Approximately equal affinities were observed in two cases of human colon carcinoma, in one human renal carcinoma, and in the rat-liver carcinoma. The other human renal carcinoma showed greater affinity for the conjugate than did the corresponding normal material. The soluble tissue proteins appeared to bind roughly half their own weight of RB200-conjugated N.R.G. and could bind all the conjugate when they were present in excess (4 parts tissue protein to 1 part conjugate). All the results of electrophoresis agreed with the histological staining reactions by the conjugated N.R.G. Because the homogenate studies were carried out on "unfixed tissue," unfixed sections of the corresponding tissue blocks were examined in parallel with the usual "fixed" (alcohol-treated) material: fixation had no obvious effect on the staining apart from occasional improvement of histological definition.

These results suggest that the soluble cytoplasmic components are concerned in the non-specific fluorescent staining of normal and tumour tissue.

Discussion

The trend of these results is towards equal staining of normal tissue and benign tumours, and diminished staining of carcinomas. Although we have followed the published methods of King *et al.* with great care, we have been unable to achieve their decisive results. While the trend we have observed points to an interesting cytoplasmic difference between benign and malignant cells, the difference is so far from being clearly defined or consistent that we doubt whether the method can be usefully applied as a diagnostic test of malignancy. The procedure, which requires expensive equipment, is difficult and time-consuming and gives less histological information than routine staining methods. Certainly we have always been able to place more reliance on conventional staining of frozen sections by brilliant cresyl blue for orientation of sections and diagnosis.

It has been shown in the electrophoresis experiments that a moderate excess of soluble tissue protein is capable of binding all the conjugated globulin—that is, the affinity is not limited to a particular group of globulin molecules. Presumably some molecules have specially strong affinity because of complementary structure or high net charge, which might explain the reduction of non-specific staining by tissue absorptions in the fluorescent antibody technique. The histological staining seems likely to be due to non-specific combination of the conjugated N.R.G. with soluble constituents of cytoplasm. Furthermore, the histological study showed that conjugated N.R.G. resembled eosin in its staining distribution; this might be a result of the net negative charge of the globulin molecule at *p*H 7.1. Such staining may be contrasted with the specific immunological staining of rat liver described in the preceding paper, in which antiserum was prepared against a microsomal-cell fraction and gave bright staining localized mainly in cell membrane and discrete cytoplasmic particles.

Summary

Investigation of the histological staining reaction of a variety of human and animal tumours with fluorescent conjugates of non-immune rabbit globulin (N.R.G.) has shown variable results with a trend towards equal staining of normal tissue and benign tumours, and diminished staining of carcinomas. The staining was never bright, and with the exception of human colon carcinoma, which stained less brightly than the corresponding normal tissue in almost every case, the differential staining was not consistent. The technique cannot be regarded as a useful practical test for the diagnosis of malignancy.

Centrifugation and electrophoresis experiments on homogenized samples of some tumours and corresponding normal tissues showed that the soluble rather than the particulate components are responsible for combining with the conjugated N.R.G. Combination can take place with all the conjugate, which, possibly because of its net negative charge, behaves as a histological stain in much the same way as standard acid dyes. The diffuse non-specific staining produced by conjugated N.R.G. is different in kind and degree from the bright, defined staining obtained with conjugated organ-specific antisera.

This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust. We are indebted to Professor J. S. Young, Professor W. O. Kermack, and Dr. M. G. McEntegart for helpful advice, and to Mrs. Evelyn Pirie and Miss Lorraine Rennie for technical assistance. We are grateful to many surgical colleagues at Aberdeen Royal Infirmary and Woodend General Hospital for providing surgical specimens.

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The London County Council Health Committee report that there were 177 confirmed cases of polio in London last year, and that more than 80% of those who contracted the disease had not been vaccinated. It is calculated that the rate of attack by paralytic polio in 1959 was seven times greater amongst children who had not been vaccinated than among children who had. In the last six months of 1958 the rate of attack had been five times greater. The Committee consider these figures to be most encouraging, and suggest that the improvement in 1959 may be linked with the fact that by the end of that year slightly over one-half of the children who had been vaccinated had received a third injection of vaccine. (L.C.C. Council Meeting, October 25.)

CORONARY ARTERY ANEURYSM

BY

GILBERT FORBES, M.D., B.Sc., F.R.C.S.Ed. F.R.F.P.S.
Reader in Charge

AND

ANDREW BRADLEY, M.A., M.B., B.S., LL.B.
Lecturer

Department of Forensic Medicine, University of Sheffield

Aneurysms of the coronary arteries are rare. A modest total of 70 cases have been reported between 1812 and 1957 (Packard and Wechsler, 1929 ; Scott, 1948 ; Crocker *et al.*, 1957). The condition has been attributed to congenital defect, syphilis, atherosclerosis, rheumatic fever, polyarteritis nodosa, and mycotic embolic phenomena, but many cases have remained unclassified and of unknown aetiology.

Case Report

This case came to necropsy at the instance of H.M. Coroner for the County Borough of Rotherham, arising out of the death of a boy of 9. He appeared to be a healthy boy until November 26, 1958, when he began to have occasional headaches and intermittent abdominal pain with vomiting ; he also had two attacks of fainting. His appetite was poor and he was sleeping badly. When he went to bed on December 3, 1958, he kept complaining of upper abdominal pain, then collapsed and died.

Post-mortem Findings

The body was that of a well-developed boy, 4 ft. 3 in. (129 cm.) in height. The main findings related to the heart, which weighed 184 g. (average for the age is 115 g.). There was no gross congenital defect of the heart or great vessels, and the valves were healthy. The left ventricle was dilated. The ostium of the left coronary artery was slightly thickened, though its diameter appeared to be within normal limits. The ostium opened immediately into an aneurysm of the left coronary artery, filled with laminated blood clot which was friable and loosely adherent to the wall of the artery (Fig. 1). The whole of the main trunk, the first 2 cm. of the anterior descending branch, and the first 0.5 cm. of the circumflex branch were affected by this aneurysmal dilatation. The diameter of the main trunk and descending branch at the site of the aneurysm was generally 1.5 cm., that of the circumflex branch 0.7 cm.

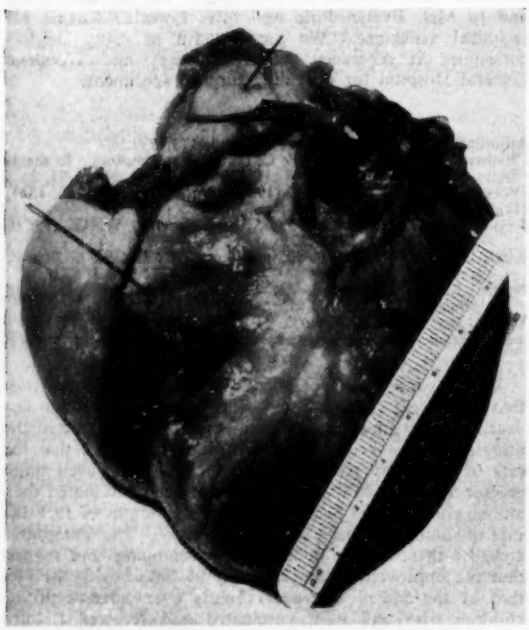

FIG. 1.—Heart, showing coronary artery aneurysm opened from the front. The white marker is in the coronary ostium.

What appeared to be the beginning of the descending and circumflex branches was marked in each case by prominent thickened rings projecting into the lumen of the sac of the aneurysm. The rings met tangentially in the acute angle between the two branches. The descending branch of the left coronary artery was blocked for some distance beyond the aneurysm by red friable clot. The right coronary artery appeared somewhat narrow. Apart from the aneurysm, the coronary arteries seemed to be healthy ; in particular, there was no tortuosity and no atheroma. The muscle of the left ventricle was tough and fibrous, and there was a prominent area of scarring of the interventricular septum measuring 4 by 2 cm. The lungs were very oedematous, there were 6 oz. (170 ml.) of clear fluid in each pleural sac, and an excess of fluid in the pericardium. There was general congestion of the abdominal organs, the spleen being much enlarged. Apart from the features attributable to the condition of the heart, there were no abnormal appearances. In particular, the blood-vessels of the organs other than the heart seemed normal.

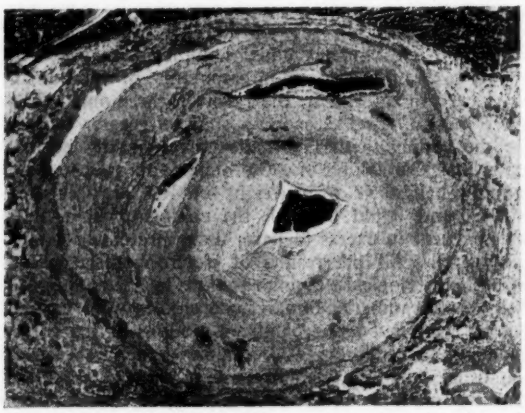

FIG. 2.—Descending branch, left coronary artery, just beyond the aneurysm. (Masson's trichrome and Verhoeff. × c. 28.)

Histology

The wall of the main trunk of the left coronary artery and of those portions of the descending and transverse branches which were the seat of the aneurysm showed gross disorganization of the intima and media. The intima was greatly thickened, and, to describe it from the inside outwards, consisted of, first, the remains of the thrombus, next a latticework of condensed fibrin, then a latticework of comparatively acellular collagen, and finally cellular fibromuscular tissue in the outermost part of the intima. Randomly scattered at various depths in the intima were some amorphous calcareous deposits. While this was the general pattern, here and there the intima had become vascularized. The muscle of the media was in general much thinned out, it was vascularized, and there was a good deal of fibrous tissue replacement. Nothing was to be seen either in the remnants of the thrombus or in the wall of the aneurysm to indicate the presence of any inflammatory reaction.

In the parts of the left coronary artery just beyond the aneurysm the intima was about five times as wide as the widest part of the media, the lumen of the vessel was extremely narrow, and the picture presented was largely one of repeated thrombosis, organization, and recanalization

(Fig. 2). The internal elastic lamina proper and the muscle of the media showed the same degenerative changes as those in the wall of the aneurysm itself, but less advanced. The absence of inflammatory reaction was again a conspicuous feature. Further examination of the left coronary artery showed that, with progression to the periphery, there was a descending order of change.

Examination of the right coronary artery disclosed that, in this artery also, degenerative changes were present. The adventitia appeared normal, but there was extreme disorganization of the other elements of the arterial wall, and it was impossible to delimit the intima from the media with any exactitude (Fig. 3).

With regard to the vascular system outside the coronary tree, unfortunately no special parts of this were removed for histological examination, so that our examination related

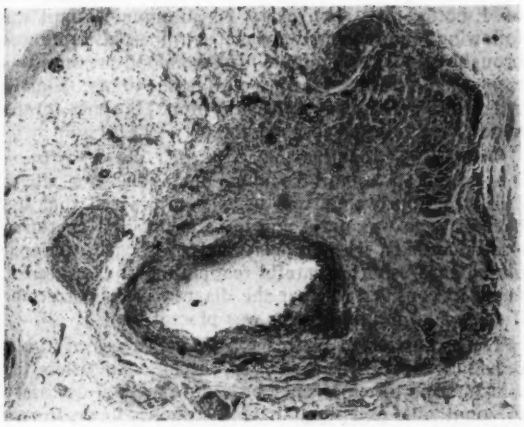

FIG. 3.—Right coronary artery at about 1.5 cm. from right coronary ostium. (M.T. and V. × c. 48.)

only to that part of the aorta attached to the heart and to such vessels as happened to be in those parts of the other organs which were removed for histology. The small vessels in the substance of the liver, spleen, pancreas, kidneys, adrenals, lungs, and brain showed no histological abnormality. The aorta also was normal.

Examination of the heart muscle in both ventricles showed only various stages and types of change associated with ischaemia. In particular, there was no change suggestive of rheumatic carditis. The histological examination of the organs other than the heart merely confirmed the conclusion reached on naked-eye examination that the changes were the result of cardiac failure.

Discussion

The cause of the aneurysm of the left coronary artery is not clear. It is obvious, however, from the findings that the process which ultimately resulted in death had been going on for a much longer period than that of the terminal illness. The large healed scar in the interventricular septum betokens an extensive infarction at least 10 weeks prior to death. The aneurysm itself must have taken many weeks to assume its final appearance. On the other hand, this boy was described as a healthy active boy. He was well-developed physically, and we feel that the process which resulted in his death could not have been going on for more than a period of months. Although it is true to say that the cause is not clear, there are a number of findings which tend to eliminate some possible causes and to favour others.

Congenital Defect.—Incomplete embryonic development of the elastica and media in medium-sized arteries, especially at points of bifurcation, has been regarded as a possible cause of aneurysm formation since Forbus (1930) made a study of cerebral aneurysms. However, the muscle of the media and the elastica were, in this case, if anything, stronger at the junction of the two main branches of the left coronary artery than anywhere else at the site of the aneurysm. Scott (1948) believes that the assumption of a congenital origin is warranted in most cases in which there are other congenital cardiovascular anomalies. In this case there were none.

Atherosclerosis.—Our opinion is that this can be dismissed as a possible cause of the aneurysm. There were no atheromatous plaques to be seen anywhere in the vascular system, and no evidence of lipid degeneration anywhere in the coronary tree.

Infectious Arteritis.—This cannot be ruled out as a cause of the aneurysm, but it must be admitted that there is no evidence of its nature or origin. There is no evidence of pericardial or myocardial infection. The picture is not that of a mycotic embolism. There is nothing to suggest bacterial endocarditis, nor do we think that syphilitic arteritis can be entertained.

Necrotizing Arteritis.—Rheumatic carditis, which has been known to cause necrotizing arteritis and coronary artery aneurysm (Rae, 1937), can, we think, be dismissed in this case. Neither the heart valves nor the myocardium showed any evidence of it. Polyarteritis nodosa, usually a systemic and diffuse disease, has been known to occur as a localized condition, and has been known to cause aneurysms of the coronary arteries (Spector, 1939; Sinclair and Nitsch, 1949). This diagnosis cannot be dismissed. The histological appearances are suggestive of a necrotic process affecting all the elements of the arterial wall, with the exception of the adventitia. It seems to us that the elastic tissue has suffered more severely than the other elements of the arterial wall. This is shown in the more peripheral sections of the arteries, where, although the muscle of the media has a normal appearance, the internal elastic lamina shows some degenerative changes. We are not aware of any destructive agent which singles out elastic tissue as its target, but we feel that degenerative changes in elastic tissue would repay closer study. Selective degeneration of the elastic tissue might explain some of the features of this case.

Summary

A case of sudden death in a boy of 9 was found to be due to localized aneurysm of the left coronary artery, resulting in thrombotic occlusion. Histological examination revealed that both coronary arteries were involved in a degenerative process affecting the intima and media of the arterial wall. The aetiology is discussed, but no definite conclusion is reached regarding the cause in this case.

We thank Professor D. H. Collins for his advice and helpful criticism in the preparation of this paper. Our thanks are also due to the late Mr. Norman S. Robson, H.M. Coroner for the County Borough of Rotherham, for permission to publish details of this case. We are indebted to Mr. S. J. Gray for the photographs.

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SELECTIVE SURGERY FOR GASTRODUODENAL HAEMORRHAGE*

BY

DAVID J. TIBBS, *M.C.*, M.S., F.R.C.S.

Reader in Surgery, University of Durham; Consultant Surgeon, Royal Victoria Infirmary, Newcastle upon Tyne

In the treatment of gastroduodenal haemorrhage the current methods of selecting patients for emergency surgery cause many of the most dangerously ill patients to be transferred to the care of the surgeon, with whom, therefore, rests considerable responsibility for bringing the overall mortality of this condition to an irreducible minimum. The success of the surgeon will depend upon such factors as the judicious selection of patients, the proper preparation of the patient for surgery, and the successful location and elimination of the bleeding-point. In 1956 we reported a study of circulating blood volumes in gastroduodenal haemorrhage and made suggestions regarding the preparation of patients for emergency surgery (Tibbs and Leslie, 1956). As a next step, it was decided to carry out a planned investigation of the surgical treatment of gastroduodenal haemorrhage to test not only the suggestions made in our previous paper but also to study other factors affecting the outcome in this form of treatment. The paper now presented reports the findings and conclusions in a group of patients treated surgically according to the principles we wished to examine.

Ideally, proper preparation and maintenance of the circulatory state during operation should permit the operation of choice to be carried out in nearly every case without undue anxiety, and this, in fact, has been our experience. Making the operation safe in this way is of fundamental importance, but attaining the object of the operation—complete control of the haemorrhage—is scarcely less important. With this in mind, the accurate location of the site of haemorrhage was attempted in all our patients. This was undertaken in order to determine how often the bleeding-point could be accurately located, and whether this was a desirable step in precise control haemorrhage.

The secondary objects of our study were to consider whether our selection of patients for operation was reasonable, to determine by long-term follow-up our success in eradicating this basic condition causing haemorrhage (as distinct from mere control of haemorrhage), and to learn the causes of failure, mortality, and morbidity.

Material and Methods

A detailed policy of surgical management was laid down at the outset, and a consecutive series of 67 patients operated upon for acute gastroduodenal haemorrhage were treated in accordance with this policy. All such patients in whom surgery was undertaken by me between the years 1953 and 1957 have been included without exception; they were all operated upon as emergencies. These cases were selected for operation on the following criteria: (*a*) They had already required 6 bottles (3,240 ml.) or more of transfused blood to maintain a reasonable circulatory state. (*b*) They were showing evidence of continuing or renewed haemorrhage (as judged by haematemesis, pulse rate, or blood-pressure) within a few days of admission to hospital; that is to say, they were not responding to the regime (basically that described by Ogilvie *et al.*, 1952) administered within the hospital.

Patients of all ages and both sexes were included; no case, however adverse, was refused operation if this course appeared to offer any prospect of saving the patient otherwise despaired for. All cases were operated on because it was believed that the bleeding came from a curable lesion of the oesophagus, stomach, or duodenum, but on occasion lesions not falling in this category were disclosed.

The patients were prepared for operation in the following way.

(1) Operation was arranged for one and a half hours after the decision to operate had been made.

(2) During the interval, blood was given at the rate of 1 bottle (540 ml.), every 20–30 minutes until the following requirements were met: (*a*) the pulse rate was brought below 100 a minute; (*b*) the blood-pressure was restored to a systolic pressure of at least 110 mm. Hg and a diastolic pressure of at least 75 mm. Hg; and (*c*) the hands were restored to good colour.

When these requirements were met the transfusion was slowed down until the actual operation. If a patient failed to improve, it was usually considered that the haemorrhage was outpacing transfusion, and operation was undertaken without delay under the cover of rapid blood transfusion; a careful reappraisal was, of course, made to consider whether the diagnosis was correct or if some complicating factor was present.

The estimation of plasma protein, as suggested in our previous paper, was not used, because so often the difficulties in the emergency procedure made it necessary to omit all excepting bare necessities; experience without its guidance was so satisfactory that we did not persist with this method.

Operation was undertaken with the intention: (1) to locate accurately the site of haemorrhage and to identify the cause; (2) to control haemorrhage by the most efficient method, preferably by excision, but as an alternative by exclusion or suture of the bleeding-point: and (3) to treat surgically the condition causing haemorrhage.

In order to reduce variable factors, only one surgeon (myself), by arrangement with my colleagues, undertook management of, and operation upon, these cases; in fact, they represent nearly all the cases coming to surgery from a medical clinic of approximately 60 beds and occasional cases from other medical wards in the hospital. Anaesthesia was administered by a restricted group of anaesthetists.

The first concern was the welfare of the patient, and, if this conflicted with the programme given above, naturally it was modified; it was, however, rarely necessary to depart to any significant degree from the routine given.

A postal follow-up was conducted recently. This was six years after the first case and six months after the most recent one.

Emergency surgery upon cases with portal hypertension was avoided as a matter of policy, and this class of case is therefore virtually excluded from this paper.

Results

Decision to Employ Surgery

The criteria of selection for surgery were designed to avoid those cases which were likely to stop bleeding

*Adapted and abbreviated from the second part of a thesis for the London M.S.

spontaneously and to select only those which, by the severity and persistence of haemorrhage, were likely to provide the fatalities of this illness.

In retrospect, the following facts were observed:

The average time between the initial haemorrhage (at home) and operation was seven days; the average time between admission and operation was four days. This suggests that reasonable opportunity to stop bleeding spontaneously had been given.

Out of 49 patients with adequate records, 33 had actually fainted from loss of blood at some stage prior to operation and another 13 had experienced dizziness or giddiness.

Out of 61 patients with adequate records, 30 had at least once before operation shown a blood-pressure below 100 mm. Hg systolic; many of these were already being protected by blood transfusion, and for a number a figure below 100 mm. Hg systolic would represent a severe drop in blood volume because the patient was normally hypertensive (Tibbs and Leslie, 1956).

Eight patients were at one stage *in extremis*, with blood-pressure unrecordable or below 50 mm. Hg systolic: only one of these died.

All patients had shown recurrent haemorrhage after admission, the unfavourable significance of which is well recognized (Avery Jones, 1947); all patients had required about 6 bottles (3,240 ml.) or more of blood and had therefore presumably bled at least to this extent.

At operation, 39 cases had a visible and often palpable artery protruding from the ulcer base. Sixteen of these were actually bleeding or bled at a touch; 11 of these bled torrentially at operation.

These points may indicate that most of these patients were liable to severe haemorrhage and either would have required a large number of blood transfusions (and on recovery still retain a potentially dangerous or symptom-causing lesion) or would have died. It is concluded that the criteria for operation provide a reasonable compromise between unnecessary surgical intervention and undue delay in coming to surgery.

Timing of Operation

Early in the series it was found that postponing the operation until a convenient time could be dangerous to the patient. It was concluded that, if the patient had demonstrated a dangerous tendency to bleed heavily and repeatedly, then operation should be undertaken as promptly as possible after a decision to operate had been made. The time of one and a half hours was chosen because it gave good time for resuscitation, cross-matching of sufficient blood to cover the operation, and preparation of a theatre and/or terminating of a preceding operation.

Time was never given for further resuscitation because if the patient failed to respond within one and a half hours, having been given adequate blood, it indicated either an urgent need for operation in order to stop the continuing haemorrhage or that the diagnosis was at fault.

Practical experience with the 67 cases made it clear that this was a sound policy: no patients were lost before or during operation, and in neither of the two patients dying withing 24 hours of operation was death in any way related to mistiming the operation or to inadequate preparation for operation (Cases 1 and 2). The majority of patients gave no real anxiety at any stage, even those in whom anaesthesia and operation were begun under cover of heavy continuous transfusion because uncontrolled haemorrhage was negating efforts at resuscitation (5 cases).

It is concluded that the policy of fixing the operation for one and a half hours after the decision to operate has been made is both practical and sound.

Pre-operative Blood-transfusion Requirements

The policy of pre-operative blood transfusion has already been described. This was designed to bring the patient to operation in the safest possible condition. The average amount of blood given pre-operatively was 2.8 bottles (1,510 ml. of citrated blood—each bottle containing 420 ml. of whole donated blood and 120 ml. of citrate solution).

Only two cases gave serious difficulties during operation.

Case 1.—A man aged 50 with a "gastrostaxis" (possibly a diffuse haemorrhagic gastritis) bled so heavily from the gastric remnant after closing the abdomen that his circulatory state was considered too critical for re-entry of the abdomen (a decision later regretted). His condition was never mastered, and after several hours and 17 pints (10.6 litres) of blood transfusion he succumbed.

This may have been an inadequate operation, but was not an inadequacy of pre-operative preparation.

Case 2.—A man aged 54 (also referred to as Case O by Tibbs and Leslie, 1956) was admitted to hospital in a moribund state, but with massive transfusion and noradrenaline a recordable blood-pressure was obtained; however, marked peripheral cyanosis was present. He was considered to be in a virtually irrecoverable circulatory state, but because repeated haematemeses of bright-red blood made it clear that heavy haemorrhage continued, operation was undertaken. This was concluded successfully with resection of the causative gastric ulcer, but his circulatory state did not improve, and he died 12 hours later.

It seems likely that a period of extreme hypotension had initiated irreversible changes and the patient had entered a state unresponsive to blood transfusion.

In all other cases operation was performed in an unhurried manner permitting the procedure of choice to be carried out.

The amount of blood transfused at operation was at the discretion of the anaesthetist, who gave sufficient blood to balance any obvious losses at operation or to achieve and maintain, so far as he could assess, a relatively normal blood volume.

Of the 67 patients, 21 showed a moderate or severe fall of blood-pressure at operation (16 of these were over 60 years of age; this may be significant, because less than half of the patients were over 60 years of age). Seven recovered their normal blood-pressure without any special measures, seven recovered their normal blood-pressure only when ouabain was given by the anaesthetist (*all* of these were over 60 years). Five improved only when haemorrhage was controlled and two with a more rapid transfusion. It would appear that the elderly myocardium may benefit from support with ouabain.

It is concluded that the policy adopted brought the patients to operation in a state that was either satisfactory or allowed safe conduct provided no complicating factor beyond immediate control was present, the cause for bleeding was adequately dealt with, and, it is scarcely necessary to say, a skilled anaesthetist manipulated blood transfusion and ouabain administration.

The average amount of blood given during and immediately after operation was 2.75 bottles (1,480 ml.). The majority of patients required no further transfusion, and it was clear that their blood-volume requirement had been adequately balanced. Thus the average

amount of blood transfusion to prepare for and conduct operation for haematemesis was from 5 to 6 bottles (2,700–3,240 ml.). It must be borne in mind that many of these patients had been maintained, so far as was possible, in a state of near normal blood volume until a further haemorrhage prompted the surgeon to take over; cases less well cared for might require a larger quantity of transfused blood to see them safely through their operation. The maintenance of a reasonable blood volume is undoubtedly the most important single safely factor in the operation.

The blood requirements were in good accord with those that might be expected from our previous blood-volume studies.

Location of the Source of Haemorrhage

The policy of seeking the source of haemorrhage as an initial step in the operation often involved a gastrotomy, and naturally the question arises whether this was really necessary or whether a "blind" gastrectomy would have sufficed when the source of bleeding was not obvious. Determination of the site of haemorrhage, or at least a guess based upon high probability, is essential for successful control of the bleeding by surgical operation. There are various possible means of determining this, and these are now considered.

Circumstantial Factors: Age and Sex

Table I relates these two factors to the lesion which was actually identified at operation; it can be seen that they provide no real help except possibly to indicate that men of over 60 with gastroduodenal haemorrhage are likely to have a duodenal ulcer. It must be concluded that age and sex alone do not enable the surgeon to predict the site of the lesion.

Clinical History

In 54 cases out of 67 the clinical history gave reliable indication of a peptic ulcer or of the actual lesion found. In patients with peptic ulcer many histories were of no use in predicting whether a gastric or duodenal ulcer would be found. Stomal ulcer was in all six cases accurately diagnosed from the known presence of a gastroenterostomy. In 10 cases the history gave no help, and in one it was actually misleading. (In two cases the history was missing from the notes.) From this experience it would appear that the history may give a positive indication of the lesion but often fail to give other than the grossest indication, and in about one in seven no indication at all. However, seven out of eight cases with histories of under two months' duration were acute gastric lesions, so that a short history should prepare the surgeon for an acute gastric lesion—often not evident from external examination of the stomach. Four out of five cases with a short history superimposed on a long history of dyspepsia were also acute gastric lesions. A prolonged history was of little value, and, as might be expected, of 42 cases with recorded long histories 12 were chronic gastric ulcers and most of the remainder were chronic duodenal ulcers. Neither of the patients with hiatus hernia gave any useful history to suggest the diagnosis. A history of consumption of aspirin preceding onset of haemorrhage strongly suggests an acute gastric ulcer (Alvarez and Summerskill, 1958); two cases with this history were bleeding from acute gastric ulcers.

One may wonder if the actual vomiting of blood at some stage excludes a lesion below the duodenum (unless, of course, a gastroenterostomy is present). It was our policy to assume that if the patient had vomited blood it was unnecessary to search for the lesion below the duodenum. Within this series of patients this held true, but as there was only one lesion—a jejunal diverticulum—below the duodenum, our experience does not permit us to draw any conclusion on the reliability of this. There are certainly exceptions; for instance, we recently encountered a patient with an aortic aneurysm bleeding into the duodeno-jejunal flexure who vomited large quantities of bright-red blood, and we have heard of other cases in which a jejunal lesion (other than a stomal ulcer) produced haematemesis. It would appear, however, that when haematemesis is included in the history a lesion below the duodenum is so unlikely that the surgeon should search carefully for a lesion in the oesophagus, stomach, or duodenum before considering the infra-duodenal portion of the alimentary tract. Out of 63 cases with clear records on this point, 59 had had haematemeses and 4 showed melaena only—the latter included the jejunal lesion. A patient with melaena only and no haematemesis should be distinguished by the surgeon, because if, on laparotomy, the source of bleeding is obscure, a search of jejunum and below should perhaps have priority, and certainly a "blind" gastrectomy should *not* be undertaken: here positive identification of the bleeding-point is imperative.

Location of the Lesion at Laparotomy

The following observations are based on the fact that, in all cases but one, positive evidence of the site of bleeding was obtained during operation; in those cases in which the bleeding-point was not actually seen at operation the presumptive evidence of external examination or palpation through a gastrotomy was confirmed by examination of the specimen.

Out of the 67 patients, 41 (Table I) showed obvious evidence of the likely source of their haemorrhage from simple inspection and palpation of organs in the upper abdomen at laparotomy. In only one of these was this evidence misleading; in this patient the duodenum showed external evidence of an ulcer, and gastrectomy was performed; the specimen showed an acute gastric ulcer, until then unsuspected, in the centre of which was an obvious bleeding-point. It is concluded that external evidence of peptic ulceration may be accepted as indicating the site and cause of bleeding; this evidence may be gross or, at the other extreme, no more than a small but highly significant area of recent adhesion formation, stippling, or a covering of fibrin.

In 26 cases there was no external evidence of the probable site of bleeding. In all these cases we were able to determine the bleeding-point by means of a gastrotomy, duodenotomy, or oesophagotomy, with the exception of the case of hiatus hernia referred to later. In four of these cases an acute gastric ulcer required a gastrectomy at a higher level than would usually be performed; it is believed that a "blind" gastrectomy might well have failed to control haemorrhage in these cases. A gastrotomy may occupy 10 minutes' time and is perhaps an inelegant procedure, but, in fact, in our experience it did not unduly complicate the operation or cause any appreciable wound-sepsis rate.

It is concluded that gastrotomy enables exact location of the bleeding-point to be made in nearly every case; it is not essential, but it is highly desirable if the first object of the operation, control of haemorrhage, is to be achieved with certainty.

Gastrotomy

In 25 cases gastrotomy was performed (Table I). The technique used was as follows.

The stomach was partially delivered and appropriately packed off with moist gauze. A 3-in. (7.5-cm.) longitudinal incision was then made in the body of the stomach; through this incision two fingers were introduced for palpation of the lesser curvature of the stomach and duodenum from within. If necessary, inspection of the interior of the stomach was then carried out. This was performed by introduction of a malleable light through the gastrotomy opening and the use of "mops on sticks" inserted deeply into the stomach, gently spreading areas of the mucosa to conduct a systematic search. With this technique, the usual ulcer-bearing area of the stomach was seen satisfactorily.

If initial palpation and inspection of the stomach interior were not successful, the gastrotomy was enlarged and a more generous view obtained or the whole hand inserted into the stomach. This permitted easy palpation of the lower oesophagus from within. In several cases the larger incision allowed the stomach to be everted to give an extraordinarily comprehensive view of the mucosa. Incidentally, a wide gastrotomy allowed massive blood clot, when present, to be scooped out or the demonstration of additional ulcers above the bleeding-point if these were present.

Palpation.—Out of the 25 cases, the bleeding-point was palpable in 15. It was recognized as a minute projection which often felt no bigger than a grain of sand; its feeling is quite distinctive, however (Bohn, 1949). The projection was, of course, a small vessel standing up in the base of a soft acute ulcer which otherwise could not have been detected by palpation. In many of these cases the bleeding-point was seen as well as palpated. Table I gives further details. In three cases of duodenal ulcer, the presence of the ulcer was appreciated only by palpation from within the duodenum via the pylorus.

Inspection.—In the remaining 10 cases the bleeding-point was demonstrated visually in all excepting one (Case 3). When the bleeding-point had been located, care was taken to include it in the gastrectomy performed.

TABLE I

No. of Cases	Lesion	Age: No. of Cases Under 40 Years	Age: No. of Cases 40–60 Years	Age: No. of Cases Over 60 Years	Sex: M	Sex: F	Lesion at Laparotomy: Externally Evident	Lesion at Laparotomy: Not Externally Evident	Gastrotomy: No. of Gastrotomies Performed	Gastrotomy: Lesion Palpated as Minute Projection	Gastrotomy: Lesion Visualized but Not Palpated	Operations Performed	Deaths and Cause
14	Acute gastric ulcer	3	9	2	6	8	2	12	13	10	3	13 Billroth I 1 wedge excision	
7	Chronic ,, ,,	1	3	3	4	3	7					6 Billroth I	1 pulmonary embolus (aged 80) 1 "irreversible shock" due to hypotension (aged 54)
2	Acute duodenal ,,	1		1	1	1	1	1	1		1	1 Polya 2 ,,	
26	Chronic ,, ,,	2	9	15 all male	22	4	23	3	3	3		24 ,,	1 recurrent haemorrhage (aged 80) 1 leaking duodenal stump (aged 64) 1 plastic peritonitis of uncertain origin (aged 76)
1	Massive duodenal ulcer and oesophageal ulcer	1			1		1					2 duodenotomies, suture of bleeder and gastro-enterostomy Total gastrectomy	
6	Stomal ulcer ..	1	2	3	5	1	1	5	5	2	3	4 suture and vagotomy 1 Polya 1 Billroth I	1 necrosis of gastric remnant with leak (aged 69)
2	Hiatus hernia ..				1	1		2	1 gastrotomy and 1 high gastrotomy in same patient on separate occasions	Lesion located at second operation		1 (*a*) Billroth I, (*b*) repair and vagotomy 1 repair and vagotomy	
1	Hiatus hernia and portal vein thrombosis			1		1		1	1 oesophagotomy			Oesophagotomy, local suture, and hiatal repair	1 hepato-renal failure (aged 68)
2	"Gastrostaxis"		2		1	1		2	2		2	2 Polya	1 uncontrolled haemorrhage (aged 50)
1	Neurolemmoma ..		1			1	1					Billroth I	
1	Torsion of gastrectomy stump		1		1		1					Revision gastrectomy	1 pancreatitis (aged 47)
1	Jejunal diverticulum		1		1		1					Excision	1 pulmonary embolus (aged 55)
1	Retrograde intussusception of gastro-enterostomy		1		1		1					Polya	
1	Duodenal ulcer and rupture of oesophagus		1		1		Duodenal ulcer evident	Ruptured oesophagus not evident				,,	1 mediastinitis (aged 48)
1	Gastric carcinoma		1			1	1					Nil	
67	Total ..	9	31	27	45	22	41	26	25	15	9	66	11 (7 with peptic ulcer)

Complications.—3 burst abdomens, 1 subcutaneous separation of incision, 4 post-operative bleeding (not from original lesion). 1 left subphrenic collection of bile, 1 pulmonary embolus, 3 lung collapse, 1 lung infection, 3 post-operative anaemia, 2 wound infections, 1 bedsore. 2 heart failure.

Significance of Hiatus Hernia

In one case gastrotomy failed to reveal the cause of bleeding; this was early in our experience, the presence of a palpable hiatus hernia receiving insufficient attention.

Case 3.—A man aged 69 gave no helpful history, and at laparotomy no lesion was evident externally but a hiatus hernia was palpated. Gastrotomy revealed no abnormality—in spite of this a gastrectomy was performed (unwisely). Two days later the patient's life was again endangered by copious haemorrhage, and after the usual preparation he was taken to the theatre for further operation. On this occasion proceedings were started with oesophagoscopy, and blood was seen coming from the region of the cardia. At laparotomy a high gastrotomy was performed and two small erosions close to the cardia were identified and sutured; a vagotomy was performed, the hiatus hernia repaired, and the left gastric artery divided at its origin. The patient made an excellent recovery.

Two other cases of hiatus hernia were encountered; in one, the lack of any helpful history caused oesophagoscopy to be undertaken as a first step and the lesion was correctly identified by seeing a bleeding area. This was treated successfully by vagotomy and repair of the hiatus hernia; the ulcer was not sutured. The other case deserves more consideration.

Case 4.—The patient was a woman aged 65. No helpful history—abrupt onset of heavy haemorrhage with haematemesis three days previously. Laparotomy revealed a large hiatus hernia, and oesophagotomy revealed two shallow oesophageal ulcers, one of which was bleeding; both were sutured. Ten days later the patient again had heavy haemorrhages; she went into gradual liver coma and renal failure, and died two weeks later. At necropsy the operation site was in good order, but a recent thrombosis of the portal vein was found; in spite of this, the abdominal viscera looked remarkably normal.

It is probable that in this patient oesophageal haemorrhage was the product of the two conditions, hiatus hernia and an acute portal hypertension. Even if diagnosis had been complete at operation, the eventual outcome would probably have been unaffected, although another procedure might have been chosen. This case comes as a reminder of the frequency with which hiatus hernia coexists with another lesion and the care with which its presence must be interpreted.

It is interesting that Case 3 is the only one in which a gastrectomy was performed in the absence of a clear indication of the site of haemorrhage and the only one in which the bleeding-point was missed completely at the first operation. The error made was due to unfamiliarity with the best course under these circumstances, and this experience led to a greater inclination to start the operation with an oesophagoscopy. Disclosure of an obvious hiatus hernia at a laparotomy for haemorrhage in the absence of any other obvious lesion should make the surgeon regard this as the cause of haemorrhage until proved otherwise; he may interrupt proceedings to perform an oesophagoscopy, but our own course of action, having come this far, would be to perform a high gastrotomy or even an oesophagotomy to identify and suture the bleeding-point. If another lesion is evident in addition to hiatus hernia, then it seems clear that the logical course is to inspect first whichever is the easier to visualize.

Upon consideration of this particular dilemma, it is concluded that a "blind" gastrectomy is quite unjustifiable in the presence of a hiatus hernia. Hiatus hernia is the likely cause for haemorrhage if no other lesion is demonstrated, but the harmless existence of hiatus hernia in the presence of another lesion is well recognized, so that hiatus hernia must not be accepted too readily as a cause for haemorrhage. This problem need not arise if oesophagoscopy is employed in any patient in whom the symptoms are suggestive of hiatus hernia or in whom there is no satisfactory history of premonitory symptoms.

Elimination of Further Haemorrhage

In most cases the causative lesion was readily excised in its entirety by an appropriate gastrectomy, but in several elderly patients with massive duodenal ulcers excision or exclusion of the ulcer would have involved a real danger of damaging the pancreatic duct (Bentley, 1952).

Early in the series this situation was dealt with unwisely in one case by leaving the ulcer undisturbed within the duodenal stump of a Polya gastrectomy; there was no bleeding from the ulcer at the time. Three days later the patient died of a torrential recurrent haemorrhage. This experience is not rare, and where an ulcer is left in the duodenal stump a determined effort must be made to reduce the likelihood of renewed haemorrhage. (The hesitation in reoperating on the patient just referred to was greatly regretted: a short period of indecision lost any opportunity of saving the patient. It would have been better to initiate immediately a second operation when it was clear that the first operation had failed to control haemorrhage.)

In 13 cases the duodenal ulcer was so massive that it was considered dangerous to attempt its exclusion, let alone its excision. In all these cases the offending vessel was readily seen through a longitudinal duodenotomy or through the transected duodenum. In eight cases it was actually bleeding or started to bleed at a touch. In all cases except one the vessel was deliberately underrun with sutures whether it was bleeding or not; the exception provided the fatal recurrent haemorrhage already referred to; none of the others showed recurrent haemorrhage. The sutures were of strong linen placed deeply with a stout Mayo needle. The duodenum was closed by sewing a flap of anterior duodenum across the lowest accessible point of the ulcer and then turning in the two "dog ears"; finally, the medial edge of the ulcer was sutured to the inturned anterior duodenal wall. We found this a practical and safe procedure, and in our hands was more adaptable than Yudin's snail closure; it is, of course, a variant of the method suggested by Tanner (1950a).

Bleeding stomal ulcer in patients with gastroenterostomy was treated in two cases by an appropriate excision of the stoma and a gastrectomy; in a further four cases the stomal ulcer was exposed by an anterior gastrotomy and locally excised or sutured, and a vagotomy was performed. Gastrectomy produced an unexpected fatality in one case from separation of the gastroduodenal anastomosis (post-mortem examination showed necrosis of stomach due to excessive mobilization). Local suture and vagotomy produced a case of haemorrhage from a recurrent ulcer 18 months later. However, the bleeding stomal ulcer is probably best treated by local suture or excision and vagotomy because of the safety and simplicity of this procedure.

One patient with "gastrostaxis" died from uncontrolled haemorrhage a few hours after operation (Case 1).

To sum up, haemorrhage was not controlled adequately or permanently in four cases. (1) A massive

duodenal ulcer left within the duodenal stump. Fatal recurrent bleeding from the causative vessel (the gastroduodenal artery) because this was not sutured. (2) A hiatus hernia to which bleeding was not attributed at the first operation; this was successfully treated by a second operation. (3) A case of hiatus hernia, oesophageal ulceration, and portal-vein thrombosis with renewed bleeding after 10 days and fatal outcome from hepatorenal failure. (4) A "gastrostaxis" (the diagnosis was accurately made but the surgical procedure was inadequate for the situation); outcome fatal.

Table I gives an account of the various lesions encountered and the operations performed.

Our general conclusion based on this experience is that accurate identification of the bleeding-point and its excision, or its ligation by stitching, with control or exclusion of gastric-acid secretion, will give a high rate of success in controlling haemorrhage. Procedures designed to control ulceration but leaving the bleeding-point to chance are certain to allow continued or recurrent haemorrhage in some cases, and must be regarded as failing to achieve the objective—namely, secure control of haemorrhage.

Should there be continued haemorrhage, a second laparotomy, if possible, probably offers less risk than conservative treatment. The first operation has been inadequate and must be completed.

Removal of Clot from Stomach

The gastric bleeders provided the largest clots within the stomach, and often it was useless to attempt aspiration of this via a stomach-tube. It was felt to be unwise to leave a large clot, for fear that it might be vomited and inhaled in the post-operative period. These clots were removed by sponge forceps through the gastrotomy, if performed, or extruded through the transected pylorus by means of appropriate pressure after mobilization of the stomach; the latter course enabled ejection of the clot to be carried out cleanly into a dish. These procedures proved satisfactory, and we believe them to have been worth while.

Mortality

Immediate Outcome of Operation.—Table I shows the findings at operation, the definitive operation performed to treat the lesion causing haemorrhage, and the consequent mortality and complication rate.

All deaths within hospital came to necropsy. In this group of patients with gastroduodenal haemorrhage treated surgically there were at least two deaths, and possibly a third, attributable to the operation itself. This contrasts sharply with the absence of any fatality amongst the last 100 consecutive gastrectomies for uncomplicated gastric or duodenal ulceration performed by me. Three factors, apart from chance, may account for this.

1. *Age of Patient.*—The three deaths referred to above were due to breakdown of a gastroduodenal anastomosis, to a leaking duodenal stump, and to a peritonitis of uncertain origin in patients aged 69, 64, and 76 respectively. Old age would certainly provide less capacity to survive a complication of this magnitude and might possibly make such complications more likely by reason of diminished vitality and rate of wound-healing. The state of these patients prior to operation, particularly with regard to nutrition, was, of course, unknown. Swynnerton and Tanner (1953) give clear evidence of the adverse influence of age in patients operated on for gastric ulcer; in their experience each successive decade after 40 years showed an increasing mortality rate. Their figures of 15.9% for patients aged 60–70 years and 42.9% for those aged 70–79 were derived from a series which included the war years, but do give an indication of the inherent influence of old age. Fraenkel and Truelove (1955), Stewart *et al.* (1956), Avery Jones (1957), and Cates (1959) all produce evidence of the adverse effects of age on either the medical or the surgical treatment of haematemesis. Death among those treated medically is most commonly due to associated conditions such as chest disease rather than haemorrhage (Avery Jones, 1956).

2. *Effect of Blood Loss.*—As will be seen when post-operative complications are considered, there was a strong suggestion of delayed wound-healing in patients who had lost a large quantity of blood, replaced by transfusion. Incidentally, the haemoglobin of the patient who died from burst duodenal stump was 22% on admission to hospital.

3. *Fatigue of Surgeon.*—This is a factor that should not be underrated. Many of these operations were done in addition to a full day's work. The surgeon's precision and judgment may be impaired under these conditions; it is as well to recognize this, particularly as these operations are often more exacting than a routine gastrectomy: the surgeon must actively remind himself to take especial care to leave all parts with good blood supply and to obtain high-quality closure of the duodenum; there is likely to be little latitude here.

Complications

The complication rate (Table I) was higher than with the usual run of gastrectomies for uncomplicated peptic ulcer, and the same factors producing increased mortality may have been responsible.

Burst abdomen or subcutaneous separation of the incision did not occur in any of the last 100 consecutive "cold" gastrectomies performed by me; we believe that delayed healing followed haemorrhage, and the very thin fascial layers in the abdominal wall of many elderly patients, unable to hold sutures well, combined to produce the four cases observed. The ages of the patients concerned were 72, 75, 76, and 76 (all survived). These cases occurred early in the series, and, after they had occurred, multiple deep tension sutures passing through all layers of the abdominal wall were employed in all patients aged over 65, or if the fascial layers of the abdominal wall were considered to be poor material; after the adoption of this routine, no more cases of burst abdomen or subcutaneous wound dehiscence occurred. The secure closure of the abdominal wound was thought to be of especial importance because our policy was that, the older and more feeble the patient, the sooner ambulation should begin. Most patients were taking a few steps within 48 hours of operation (Asher, 1947).

The mortality and morbidity recorded in Table I may at first sight be thought to be unduly high, but it must be remembered that no patient, however unpromising, whose life was endangered from haemorrhage was refused operation if this appeared to offer the best chance of survival. The fact that two cases went into heart failure, sufficient to cause anxiety, within a few days of operation is some indication of the class of patients included in this series. By reason of the method of selection of patients and my declared interest, this series was strongly biased with poor-risk patients.

Blood Transfusion

The number of blood transfusions given to patients to sustain them through their illness from the time of admission to the medical wards to their discharge from their surgical wards was 11.2 bottles per patient (6,040 ml.) (based on 28 records). This figure perhaps indicates that surgical management of gastroduodenal haemorrhage for patients selected on the basis described—that is, heavy persistent bleeders—is economical of blood transfusion. This in itself may constitute a factor-deciding operation in patients with rare and valued blood groups such as A rhesus negative. This applies to one of our patients in whom the decision for operative treatment was made after she had required 4 bottles (2,160 ml.) of blood in the medical wards. There was a regional shortage of her blood group at that time, and operation was undertaken to limit her loss, not only because rhesus-positive blood might have had to be resorted to in the event of continuing blood loss, but also because group A rhesus-negative blood might have been needed urgently for a maternity case.

Follow-up

The 56 patients leaving hospital were followed up by out-patient clinic and by postal inquiry; two patients could not be traced. Table II summarizes the findings, and the following facts were revealed.

(*a*) There were three cases of a further gastroduodenal haemorrhage.

TABLE II.—*Long-term Follow-up*

Survivors Leaving Hospital	Original Lesion	Gastric Symptoms	Deaths after Discharge from Hospital
14*	Acute gastric ulcer	3 "small stomach" } all 1 "dumping" } mild	
5	Chronic gastric ulcer	1 fairly marked—sense of epigastric heaviness; has multiple other unrelated symptoms	1—unrelated cause, 2 years later (aged 78)
2	Acute duodenal ulcer	1 has required further operation for stomal ulcer 1 mild epigastric discomfort	
23	Chronic duodenal ulcer	4 mild	2—unrelated causes: 9 months later (aged 79); 2 years later (aged 71) 1—recurrent haemorrhage a year later in a case treated by duodenotomy, suture of ulcer and gastroenterostomy (aged 70)
5	Stomal ulcer	1 has required a further operation for recurrent haemorrhage	1—unrelated cause, 1 month later (aged 76)
2	Hiatus hernia		
1	Retrograde intussusception of gastroenterostomy	1 "afferent-loop" syndrome; has required further operation	
1	"Gastrostaxis"	Required further operation for haemorrhage from a neurofibroma at stoma	
1	Gastric carcinoma	Died 2 months later	
1	Neurolemmoma	Living abroad; reported to be well	
1	Duodenal ulcer and oesophageal ulcer	Did not reply to questionary; known to be comparatively well and without gastric symptoms	

* Two of these patients could not be traced.

Summary: 56 left hospital: 2 untraced, 6 died since leaving hospital, and 48 cases traced (44 satisfactory and 4 unsatisfactory and required further surgery).

Case A.—A man aged 70 died from internal haemorrhage a year after leaving hospital. At his original operation a duodenotomy, suture of the bleeding point, and a gastrojejunostomy were carried out. It is probable that his death was due to bleeding from a stomal ulcer and that it indicates the undesirability of the procedure adopted in this patient.

Case B.—A man aged 40 was readmitted to hospital with haematemesis a year after operation; this had been for haemorrhage from a stomal ulcer which was locally excised and a vagotomy performed. A second operation revealed a persisting strand of vagus nerve, and this was divided. The patient remained well one year later.

Case C.—A woman aged 51 was readmitted to hospital because of anaemia, episodes of haematemesis, and persistent occult blood in stools. At the original operation a Billroth I gastrectomy had been performed for multiple gastric erosions. A further operation was undertaken, and haemorrhage was found to be arising from a small polyp-like projection removed from the anastomosis. Histological examination showed it to be a neurofibroma. The patient remained well one year later.

(*b*) In addition to the death already mentioned, five other patients had died. One, aged 76, had died from heart failure one month after leaving hospital. Three patients had died nine months, two years, and two years respectively after leaving hospital, from causes other than gastroduodenal haemorrhage; the ages of these patients were 79, 78, and 71 years respectively. A patient with gastric carcinoma died soon after leaving hospital.

(*c*) The remaining 46 patients were questioned at periods varying from six months to six years after their operation. Eleven patients complained of mild or moderate symptoms typical of any gastrectomy series; two had severe symptoms and required further operation—one for stomal ulceration and the other for afferent-loop syndrome.

We conclude that the cure rate of the original condition causing haemorrhage may be slightly less favourable than with elective operations for uncomplicated peptic ulceration, but in most patients a good long-term result can be expected in spite of the circumstances of the operation.

Pathology Note

Twenty-one cases out of 67 were due to bleeding from gastric ulcers. Seven of these were more than 1 cm. across and had a firm fibrous base; these were thought to be chronic. The remaining 14 ulcers had every appearance of being of very recent origin, because they were shallow, lacked induration, and varied from a few millimetres to 1 cm. across; they were either single or multiple, were situated close to the lesser curve, and those that had bled had a small artery protruding from the base.

There was evidence that these 14 acute lesions were associated with a well-established atrophic gastritis. Some of the earlier specimens were not examined histologically for this particular point, but Dr. R. O. K. Schade reports that, histologically, 10 cases showed clear evidence of atrophic gastritis, and three of these had widespread intestinal metaplasia. Avery Jones (1947) found gastroscopic evidence of mucosal atrophy in 16 out of 38 cases of acute gastric ulcer.

Many of the patients with atrophic gastritis complicated by a shallow bleeding ulcer gave a history of vague dyspepsia for some years, but more than half of these patients gave as well a recent history of only a few days of epigastric pain of moderate severity. Of 12 patients giving this history, 10 had one shallow gastric

ulcer or more. Avery Jones (1947) drew attention to the association between a brief history and haemorrhage from acute gastric ulcer demonstrated by the gastroscope. The clinical picture of a brief history culminating in haemorrhage seems typical of atrophic gastritis complicated by a shallow ulcer.

Discussion

It is unprofitable nowadays to compare the results of medical and surgical treatment of gastroduodenal haemorrhage—one is complementary to the other, and surgery will (and should) inevitably collect many of those cases likely to provide the fatalities; few patients should die from haemorrhage without an attempt at saving them by surgery. Our own experience in this respect is interesting.

A survey was made of all the deaths associated with admission for haemorrhage from peptic ulcer in two medical wards consistently referring cases to us over the period 1953–7. During this time 392 patients were admitted for gastroduodenal bleeding, and 47 of these were transferred for surgery and are included in the present series. Among the 345 patients remaining in the medical wards, three deaths occurred from associated disease (coronary thrombosis, basilar artery thrombosis, and bronchopneumonia) and two from haemorrhage so violent that there was no opportunity of saving the patient by surgery; no deaths preventable by surgery occurred among these five patients dying on the medical wards. This perhaps indicates a high degree of success in selecting patients for surgery, and we have already indicated the reasons why we consider that surgery was not overused in this series. The overall mortality rate for the 392 patients just referred to, including those that came to surgery, was 3%. Our findings and results are in general accord with those of Bohn (1949), Tanner (1950b, 1951, 1954), Ogilvie *et al.* (1952), Fraenkel and Truelove (1955), Avery Jones (1957), and Cates (1959), and we do not propose to analyse further the features of the entire group medically and surgically treated.

Perhaps the question, "Is surgery employed too seldom?" should be asked. Our observation that no patients died on the medical wards for lack of surgery makes it hard to see how more frequent employment of surgery could lower the mortality rate any further.

It is just possible that a few "medical" deaths might be prevented by the advantages of early ambulation and the shortened illness offered by surgery. These problematical advantages would scarcely justify the increased administrative difficulties arising from reorganization of the average hospital to accommodate more emergency major operations of this type; it would probably be an unwise deployment of our hospital resources. Moreover, the surgery of gastroduodenal haemorrhage is often exacting, and certainly requires an experienced operator if it is to retain its advantage over medical treatment in selected cases; widespread adoption of indiscriminate gastrectomies for haemorrhage might well lead to a dilution of the skill employed. There is a risk in surgical treatment which is accepted only because, by present selection, it is considered far less than the risk of continuing with medical treatment. It seems that increasing the number of emergency gastrectomies for haemorrhage cannot be justified.

One problem that continues to arouse controversy is the matter of a "blind" gastrectomy. Bruce and Dudley (1959) produce good evidence that in cases in which laparotomy reveals no obvious source for the haemorrhage a "blind" gastrectomy will usually prove successful. Our study, however, confirms their own observation that in an occasional case haemorrhage will not be controlled by this means, and we have suggested at least two circumstances as direct contraindications to a "blind" gastrectomy. Moreover, our experience shows that in most cases the bleeding-point can be located with certainty. It is not our intention to condemn outright the "blind" gastrectomy but rather to emphasize its shortcomings and to indicate that by gastrotomy, with simple palpation within the stomach, we can obtain a quick and sure location of the point of bleeding in over half the patients in whom, otherwise, gastrectomy would be "blind." A "blind" gastrectomy may be justifiable as a carefully considered decision, but one cannot feel enthusiastic towards it as a routine policy, particularly as the alternative procedure of a preliminary gastrotomy can so easily resolve all doubts or, in the occasional case in which it fails to reveal the source of haemorrhage, warn the surgeon that he should think again before proceeding with gastrectomy.

Summary

A group of 67 patients with gastroduodenal haemorrhage were selected for operation on the basis of the amount of blood transfusion already needed to maintain good condition and the presence of persistent or renewed haemorrhage after admission to hospital. This resulted in a reasonable compromise between unnecessary eagerness to operate and undue tardiness.

A defined policy of pre-operative transfusion to restore certain minimal clinical requirements and of arranging a set time for the operation was found to be both practical and satisfactory.

At operation the site of bleeding was demonstrated in all cases either by exterior evidence of peptic ulceration or by palpation and visualization through a gastrotomy; in one case a second operation was necessary to accomplish this.

By gastrotomy it was found possible to detect the bleeding-point in virtually every case in which the bleeding was gastric or duodenal in origin. In several cases a bleeding gastric ulcer situated above the upper limits of the usual gastrectomy was found; a routine "blind" gastrectomy might well have missed these lesions. It has been concluded that a blind gastrectomy is seldom necessary and is to be avoided, particularly in the presence of hiatus hernia or in patients with a history of melaena only.

The most effective methods of controlling the bleeding-point have been discussed and the necessity stressed for securing the bleeder in some fashion.

Long-term follow-up showed that it was possible, in most cases, to cure the condition causing haemorrhage.

The clinical picture of haemorrhage with a short dyspeptic history was found to be very suggestive of atrophic gastritis.

An overall mortality rate of 3% was found for a group of 392 patients admitted for gastroduodenal haemorrhage and treated either medically or by surgery in cases selected by the criteria given.

I thank the physicians of the Royal Victoria Infirmary for their most friendly collaboration. My anaesthetist colleagues have been partners in a rewarding enterprise, and I should like to record my appreciation of their unfailing co-operation and to acknowledge my dependence upon

their skill; in particular I am indebted to Professor E. A. Pask, Drs. M. H. Armstrong Davison, A. Mackenzie, J. A. G. Horton, and J. S. Inkster for their help in this respect and for many valuable suggestions and much information incorporated in this paper. I am grateful to Professor A. G. R. Lowdon for his encouragement, advice, and helpful criticism.

The treatment of the patients referred to in this paper required at least 700 bottles of blood, and I should like to express, on behalf of these patients, their debt of gratitude to the blood donors and to those who collected and cross-matched all this blood without error.

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INFECTIVE HEPATITIS IN A MIXED SCHOOL, WITH HIGH ATTACK RATE IN FEMALES

BY

J. H. MacDONALD TILLEY, M.A., M.B., D.P.H.
Late Assistant Medical Officer of Health, Lancashire County Council, Division 10; Assistant Medical Officer of Health, City of Oxford

A small epidemic of infective hepatitis in an urban district of the County of Lancashire consisted almost entirely of girls at one mixed school, although there was no great excess of girls in any one class at the school.

Pickles (1939), in his classical description of infective hepatitis in rural Yorkshire, does not give any figures showing that females are specially susceptible to this disease.

MacCallum *et al.* (1951) reprint tables for Denmark (1928–45) and Sweden (1931–7)—countries in which the disease was nationally notifiable—and also for their special area of study, the wartime Eastern Region of England, where all types of jaundice were made notifiable in November, 1943. Again there is no mention of differences between the attack rates for the two sexes; for example, an excess of female cases in the Eastern Region "was due almost entirely . . . to the absence of adult males on active service."

The factors in the Lancashire school epidemic were analysed, and finally compared with figures quoted by MacCallum *et al.* (1951), which refer to large numbers of pupils and schools.

The Epidemic

A semi-urban community of about 10,000 in the south-west of Lancashire was served by three primary schools, of which one, X, traditionally took its pupils from a well-localized area in the township.

After a period of freedom of six months or more the first three cases of infective hepatitis occurred in January, 1959. They were all pupils at school X. The epidemic came to an end in June; no new cases were reported up to the beginning of 1960.

In all, 30 cases were notified by the school welfare officer, health visitors, and general practitioners—jaundice was voluntarily notifiable from May 22—or were discovered by me on the home visit made to each case. Of these, 29 were school-children, of whom 27 attended school X. Conversely, among the 87 household contacts of these 29 children jaundice or suspicious symptoms occurred only once. Among the 86 contacts who escaped clinical infection were 23 of school age; 8 attended secondary schools and 6 primary schools other than X. Evidently this was a true school epidemic.

However, some of the 27 pupils of school X may have been infected by a sibling attending the same school—that is, when the second child fell ill 15 to 40 days after its sibling. In 13 households only one child per household was affected; in another six households hepatitis attacked two children in each, the interval between the two illnesses being 0, 4, 15, 18, 29, and 95 days respectively. In the last household two children and the father fell sick, with an identical interval of 27 days between each of the siblings, and between the second sibling and father.

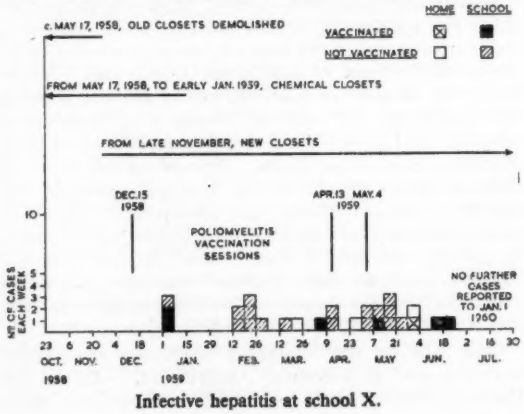
We have therefore the alternative of 27 "school" cases, or 23 "school" cases and 4 "home" cases.

Age and Sex Incidence.—No personal or household history suggesting hepatitis was obtained from any teacher, school-meal-service helper, or workman on the premises. There was a high female attack rate (Table I).

For comparison, an outbreak of mumps in October/November, 1959, involved 15 girls and 8 boys, a distribution which I find could have arisen by chance once in 3 to 5 situations.

Evolution of Epidemic.—There is a three to four weeks' periodicity of number of cases against time (see Graph).

Relation to Vaccination against Poliomyelitis.—Groups of children were given their first or second injection on December 15, 1958, April 13, 1959, or May 4, 1959. The last two sessions were held when the weekly report of the school welfare officer had shown no absences due to jaundice for at least six weeks. This was an inadequate precaution (see Graph);


HOME SCHOOL
c. MAY 17, 1958, OLD CLOSETS DEMOLISHED
VACCINATED
NOT VACCINATED
FROM MAY 17, 1958, TO EARLY JAN. 1959, CHEMICAL CLOSETS
FROM LATE NOVEMBER, NEW CLOSETS
DEC.15 1958
APR.13 MAY.4 1959
POLIOMYELITIS VACCINATION SESSIONS
NO FURTHER CASES REPORTED TO JAN. 1 1960
NO. OF CASES EACH WEEK
10
5
4
3
2
1
23 6 20 4 18 1 15 29 12 26 12 26 9 23 7 21 4 18 2 16 30
OCT. NOV. DEC. JAN. FEB. MAR. APR. MAY JUN. JUL.
1958 1959

Infective hepatitis at school X.

TABLE I

Age in Years:	<5	5	6	7	8	9	10+	Total	Total All Cases	Expected Numbers: School cases only	Expected Numbers: All cases
No. of girls	10	17	23	23	18	15	17	123			
No. of girls with hepatitis "School" cases	3	4	4	3	1	2	4	21	23	12·3	14·5
No. of girls with hepatitis "Home" ,,	0	0	0	0	1	0	1	2			
No. of boys	6	12	13	21	18	20	17	107			
No. of boys with hepatitis "School" cases	0	0	0	2	0	0	0	2	4	10·7	12·5
No. of boys with hepatitis "Home" ,,	1	0	0	0	1	0	0	2			

These figures are highly significant. Counting 27 "school" cases, $\chi^2 = 10{\cdot}96$ with 1 degree of freedom, whence $P \simeq 0{\cdot}001$. Counting 23 "school" cases, $\chi^2 = 13{\cdot}06$ with 1 degree of freedom, whence $P < 0{\cdot}001$.

absences must have been attributed to diagnoses based on pre-icteric symptoms. The records show that only 7 of the 27 cases had received an injection within the previous six months, whereas for the whole school two out of every three pupils had received at least one injection by May 5, 1959.

The intervals between the injection(s) and onset of jaundice were 17, 19, 19 (40), 25, 51 (114), 88 (155),* and 136 days respectively.

Other Factors.—Hepatitis was equally prevalent among those who ate school dinners (2 boys and 12 girls) and those who lunched at home (1 boy and 12 girls). No infestation by insects or rodents was discovered anywhere on the premises or meals centre.

Toilet Accommodation.—The original toilets were of a trough type—namely, four places and one urinal for junior boys, and four places and one urinal for junior girls and infants. In May, 1958, these were demolished to make way for a new hall, the contractor substituting chemical closets—namely, three places for boys, and three places for girls. In late November, 1958, new water closets became available—namely, two places and one urinal for boys, and four places for girls. Finally, in early January, 1959, the chemical closets were removed. Thus there was only one short period—November, 1958, to January, 1959—when toilet accommodation was adequate, in quantity at least. In the summer and autumn of 1958 great disturbance of soil and subsoil took place as a result of this work and rebuilding. However, in a school where all classes were mixed it is unlikely that this factor would operate to produce a differential attack rate.

Discussion

Exclusion of Transmission by Syringes

An attempt to sterilize the hypodermic needle *in situ* on the syringe between injections, as described by Fleming and Ogilvie (1951), met with unexpected difficulties and was abandoned. The technique used for most injections is open to criticism. A 1-ml. syringe was used to give the injection, pressure being maintained on the plunger until the needle had been replaced by another sterile needle. The process was repeated until the phial of 9 or 10 doses was empty, when the syringe was resterilized.

There is argument concerning the existence of separate viruses typically causing infective hepatitis and homologous serum jaundice respectively. Parenteral injection of blood or serum from cases of infective hepatitis has been followed by jaundice at intervals of less than 40 days in some cases (McCallum, 1955).

*This child's sibling, who had not been injected, developed jaundice four days later. Thus at most four children developed jaundice 40 days or more after an injection.

In this epidemic there was a three to four weeks' periodicity in the case incidence, and four at most of the cases developed jaundice later than 40 days after injection. Irrespective of any estimates of incubation period, only seven instead of an expected number of 18 cases followed an injection, and these were not gathered into an explosive outbreak.

Girls and boys were inoculated together in random order.

Role of Bowel-to-mouth Transmission

Inadequate or unhygienic closet accommodation causes most inconvenience to females; males can be more fastidious. The most striking effects should be obvious where: (1) closet accommodation is inadequate; (2) toilet facilities are separate for the two sexes; (3) infection is being spread through infected toilet-seats, etc., and/or perfunctory hand-washing; and (4) the disease is not exceedingly infectious and is infectious for only a short time; contact must be fairly close to spread the infection.

With regard to No. 4, Pickles (1939) says: "This disease has an astonishing behaviour in families—and in small villages that are like families—which has no counterpart in any other disease. There is what may be termed serial incidence." He also makes this interesting observation: "Wives almost invariably infected their husbands and in more than one instance their children escaped. Husbands, curiously enough, did not infect wives."

All the conditions (1) to (4) were satisfied in the Lancashire epidemic, if we assume an intestinal-oral transfer of the virus.

MacCallum *et al.* (1951) analyse three epidemics by sex and age.

(*a*) A small school epidemic (page 31): attack rates for boys and girls were almost equal. School toilet accommodation may have been adequate; outside, "pail privies were universal"; 7 out of the 26 cases may have been infected at home.

(*b*) An institutional epidemic (page 44): attack rates for age-group 5–14 again almost equal. However, the institution was one for mental defectives, and 38 out of 82 cases belonged to a very low-grade group with unhygienic habits.

(*c*) Consolidated figures for epidemics in day schools (page 13) (Table II).

TABLE II

Area and Date	No. at Risk, Ages 5–14: Male	Female	Total	Attack Rates (%): Male	Female	Total
Southend, 1943	4,300	3,924	8,224	4·5	4·2	4·4
Bishop's Stortford, 1943–4	572	460	1,032	8·2	11·3	9·6
Bungay	495	285	780	17·0	25·6	20·1

Here there is the expected type of inequality in rates when we pass from urban to rural conditions; this is not explained by an excess of females at risk in the more vulnerable 10 to 14 age-group—for example, see detailed table for Bungay (Table III).

TABLE III

Age-group (Years)	5–9	10–14	Total	Both Sexes 5–14
No. of girls at risk	126	159	285	780
Attack rates (%)	15·1	34·0	25·6	20·1
No. of girls with hepatitis ..	19	54	73	157
Expected numbers, for equal attack rates on boys and girls			57·4	
No. of boys at risk ..	142	353	495	
Attack rates (%)	12·7	18·7	17·0	
No. of boys with hepatitis	18	66	84	
Expected numbers for equal attack rates			99·6	

For the age-group 5–14 years $\chi^2 = 7{\cdot}88$ for D = 1, whence $P < 0{\cdot}01$, which is significant.

Summary and Conclusions

Under certain conditions, which are enumerated, an infection with the bowel-to-mouth type of spread should show a high attack rate in females. A school epidemic of infective hepatitis provides an example.

Bowel-to-mouth transmission of this disease has been proved experimentally in volunteers; this epidemic appears to be a demonstration in the field of the same fact.

The infection was not spread by injections of poliomyelitis vaccine given at a time when the extent of the epidemic was not realized.

I am grateful to Dr. S. C. Gawne, Principal School Medical Officer, Lancashire County Council, for permission to publish, and especially to Dr. A. C. Crawford, Divisional Medical Officer, Lancashire County Council, who suggested this paper, for help and encouragement. I am also indebted to Dr. J. F. Warin, Medical Officer of Health, City of Oxford, and to Mr. A. Barr, Chief Records Officer, Oxford Regional Hospital Board, for statistical analyses; and to Professor E. T. C. Spooner for criticisms. Finally, I wish to thank the teachers and general practitioners of Division 10, Lancashire County Council, whose co-operation enabled me to collect the material.

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"County Hall, London, has acquired five letters from Mrs. Humphry Ward, written to 'Dr. Barlow,' afterwards Sir Thomas Barlow, physician to Queen Victoria. They have been given by Miss Helen Barlow, his daughter. They are written in a clear hand, and, naturally, well phrased, and they belong to the 1898–9 season when Mrs. Ward was organizing the Tavistock Settlement, which now bears her name. She wrote to Dr. Barlow about the invalid children's school she wanted to found. She asked him to suggest a doctor for the committee, and later invited him to see the school and take tea with her. Finally she thanked him for a 'generous gift'—presumably money. The letters have a social significance, for this school for cripples became, as Mrs. Ward prophesied, 'the beginning of a general scheme for invalid children's education.'" (*The Guardian*, September 29, 1960.)

LONG-TERM FOLLOW-UP OF HYDROCEPHALIC INFANTS TREATED BY OPERATION

BY

A. R. TAYLOR, M.A., M.B., F.R.C.S.Ed.
Neurological Surgeon, Royal Victoria Hospital, Belfast

J. R. MILLIKEN, M.B.
Psychiatrist at Belfast Child Guidance Clinic

AND

P. P. DAVISON, M.A.
Psychologist at Belfast Child Guidance Clinic

Before the introduction of plastic substances which human tissues would tolerate without reaction, surgeons strove mightily, but largely in vain, to lead unabsorbed cerebrospinal fluid from the spinal canals of hydrocephalic infants to sites where it would be absorbed. Quincke (1891), Parkin (1893), and Cushing (1905) were the principal pioneers, and the German surgeon Heile from 1910 to 1927 the most persistent (Heile, 1925). For twenty years thereafter few such operations seem to have been performed, but with the addition of "polythene" tubing to surgical equipment, surgeons began again to anastomose the ventricles or the spinal theca to the ureter, mastoid cavity, peritoneal or pleural cavity, vertebral marrow, jugular vein, and many other likely and unlikely sites.

It is not the purpose of this paper to advocate any particular method, although the cases described were all treated by theco-peritoneal anastomosis. Each method has its champions, and the results overall are claimed to show from 30 to 80% of "cures" varying widely according to the definitions of hydrocephalus and the criteria for operation. Laurence (1958) followed up 182 untreated hydrocephalic infants and showed that half of the survivors were educable and potentially useful members of society. This by implication raised the question of the advisability of treating hydrocephalus surgically.

As the long-term investigation of cases operated on is limited by the small number of years in which the operation has been technically practicable, it will not be possible for a long time to assess the intelligence and social usefulness of a large surviving series. It is, however, over seven years since the first infants were operated on in this centre, and the five survivors of the eight children treated during the first year are now at school. The investigation of these children's present status by psychologist, psychiatrist, and neurological surgeon is the subject of this paper. Although the number is small, the series seems fairly representative of the larger one presenting in the following years, and the findings, although tentative, may be important.

Material and Results

Eight infants with communicating hydrocephalus were operated on during 1952, of whom three died. One developed a staphylococcal meningitis six weeks after operation. One died a year after operation, and at post-mortem examination was found to have large chronic subdural haematomata, which had probably developed in the immediate post-operative period as the result of a too sudden lowering of the intracranial pressure. One

was under treatment for gastroenteritis when the hydrocephalus was observed. After operation he died from a recurrence of this disorder.

The following are the clinical histories and present state of the five survivors.

Case 1

This baby was first seen in the premature ward of the Belfast Maternity Hospital. She was 1 week old and had been born four weeks prematurely, but without complications. Her head was expanding rapidly and measured 41 cm. in

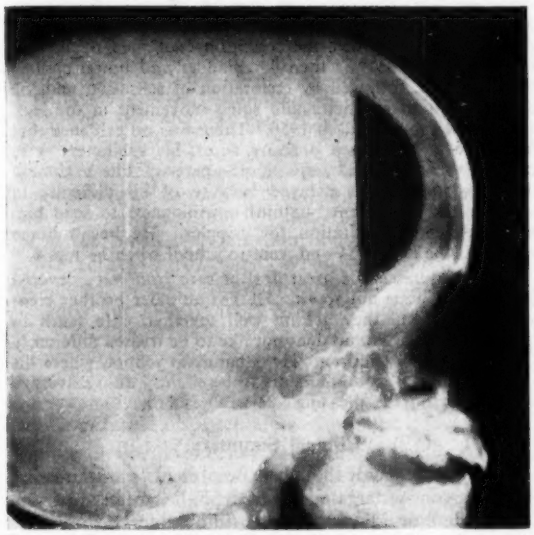

FIG. 1.—Case 1. Air study showing ventricular size, and thickness of surviving brain.

circumference. Ventriculography showed a communicating hydrocephalus with a surviving pallium 2 cm. thick (Fig. 1). The ventricular fluid was xanthochromic and the protein was 100 mg./100 ml. Operation was delayed for one week to give opportunity for spontaneous arrest or the reduction of the protein level in the cerebrospinal fluid. At the end of this time the skull circumference was 44 cm. and the protein 50 mg./100 ml. Theco-peritoneal anastomosis was performed. The fontanelles became depressed, and skull expansion ceased. At 6 months the child did not appear to see, and had constant spontaneous nystagmus. At 1 year she was standing with support and could see, but had developed an alternating squint as well as the nystagmus. The optic disks were pale. She walked and cut her teeth at the usual times and was talking well by the age of 3.

She was easily trained, but started to wet the bed again when a baby sister was born; she was then 3½. She continued to be jealous of her younger sister until she went to school, but her aggressive tendencies then came under control, and, if anything, she became shy and self-effacing. This prevented her complaining enough when she could not see the blackboard, and, as a result, she lagged behind the other pupils in arithmetic. When this was put right she improved, and is now an average pupil, holding her own in the middle of the class. Her I.Q. is 100 (Stanford–Binet). She is happy at school and makes friends easily. She tends to follow rather than lead, but likes to mother and look after smaller children. Her alternating squint is still under treatment, and the nystagmus persists. She is 7½ years old.

Case 2

This baby was born in April, 1952, by caesarean section. There had been no disproportion in a previous pregnancy, so it is likely that he was hydrocephalic at birth. The skull expanded slowly, and he was 8 months old before it was appreciated that his head was too large. He had no other symptoms. On admission the skull circumference was 52 cm. and the fontanelles were tense. Ventriculography revealed a communicating hydrocephalus with only 0.5 cm. surviving-brain thickness (Fig. 3). His lower limbs were spastic but he was otherwise normal on examination. He was operated on in spite of the thin pallium. For the first four days drainage was satisfactory and then tension built up again. The theco-peritoneal tube was inspected and found to be blocked at the abdominal end. It was replaced, and for the next three months functioned intermittently, being apparently blocked for about half the time. Thereafter drainage was satisfactory, but the skull meanwhile had expanded to 56 cm.

At 18 months he was standing with support. Other milestones were passed at the normal time. At 2 years he had a good vocabulary but his gait was spastic. At 3 years he was supplied with splints to correct his genu valgum and equinovarus. At four years his spasticity was less and his intelligence appeared to be normal. Rote learning was always above the average judged by nursery standards. He is the second child of three, and at present the most independent. He has, of course, received more attention than the other two, and, probably as a result, tends to insist on having his own way. He has already decided on a career in medicine, probably seeing the doctor as the all-powerful individual to whom even parents defer. He is friendly, and wants to join in everything, but the limitations set by the residual spasticity of his legs prevent his participation in some games. He does not seem to resent this at the present time. His teachers regard his school performance as average and his I.Q. is 104.

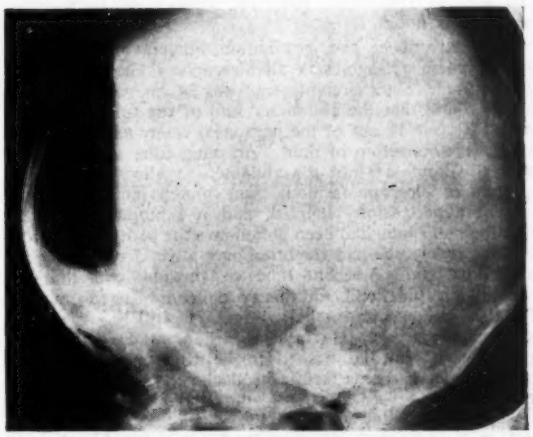

FIG. 2.—Case 2. Air study showing ventricular size, and thickness of surviving brain.

Case 3

This baby was admitted to hospital in June, 1952, at the age of 10 months. Her birth had been uncomplicated after induction at 38 weeks because of Rh incompatibility. At 5 months the parents thought the head was abnormally large, but she was not referred for examination then. At 10 months the head was still growing too quickly and she was vomiting frequently. She was then trying to hold up her head but not sitting up. She played with toys, but was thought to be a little retarded.

On examination the skull diameter was 49.5 cm. and the anterior fontanelle was widely open and tense. There were constant rotatory nystagmoid movements of the eyes but no other neurological abnormalities. Ventriculography showed symmetrical dilatation of the ventricles and no obstruction to ventricular outflow. The surviving pallium measured 1 cm. Theco-peritoneal anastomosis with polythene tubing was done. Post-operative progress was normal and the fontanelle began to close. She did not walk efficiently until she was 2 years 3 months old, and showed a tendency to genu

recurvatum, for which she was given corrective splints. At about this time there was an episode of vomiting and fretfulness for which she was readmitted. Intracranial pressure was 275 mm. Symptoms and pressure settled in three days, and she had no further trouble. During her third year she was often fretful. Walking was unsteady at times and she had a tendency towards genu valgum.

In July, 1954, the family went to Canada and the child began to attend school at the age of 4. During that year she had two generalized epileptic attacks and is still on anticonvulsant drugs. Her early school reports were encouraging, and she was said to be "82% normal." It is not known if this refers to I.Q. or is a general assessment, but she has remained in the class appropriate to her age. She works and plays happily, but apparently has aggressive outbursts. A letter from the mother says there are no domestic troubles, and referring to the child's earlier walking difficulties, that "——— can now run, skip, hop, and do the hula hoop." Her I.Q. is not known.

Case 4

This baby was born in May, 1952. His birth was normal but skull growth was probably excessive from the start. He was admitted to hospital at the age of 4 months, obviously hydrocephalic but not showing any neurological abnormalities. Skull circumference was 48 cm. Ventriculography showed a communicating hydrocephalus. Brain thickness was 0.5 to 0.75 cm. A theco-peritoneal anastomosis was done. The sutures began to close. His early milestones were passed normally, but he did not walk until he was just over 2. His behaviour and vocabulary were appropriate to his age. At 3 years 2 months he became lethargic and vomited frequently. After two weeks a left sixth-nerve paresis was noted.

On admission he had, in addition, bilateral papilloedema and a coarse nystagmus in all directions. The fontanelles were closed. Skull circumference was 54 cm. At operation it was found that the abdominal end of the tube had been pulled by growth out of the peritoneal cavity and was lying in a cystic collection of fluid. An outer tube was threaded over this, and led into the abdomen to allow for further growth in telescope fashion. One month later the intracranial hypertension recurred, and re-exploration showed that the outer tube had been pulled into the peritoneal cavity, and the inner tube had fractured over a rib, 5 cm. above its abdominal end. A second tube was threaded over the still functioning spinal end, and this system continued to function for the next two and a half years. He still had a partial sixth-nerve paresis. He went to school at 4½. This was rather early, but he wished to be with the neighbour's children. He had an attack of headache and vomiting lasting one day just before his fifth birthday, but on admission to hospital settled down completely.

In January, 1959, when he was 6 years 8 months old, he had another attack of vomiting and drowsiness, and this time developed papilloedema. A Spitz–Holter valve was used to anastomose the dilated ventricular system to the superior vena cava. He was last seen in May, 1960, then aged 8 years, and remained healthy and active. He was left-handed, and had more difficulty than his schoolfellows in learning to write, having a strong tendency to reversals. In reading and other subjects his performance was average, and his teachers were satisfied. He has one brother, two years younger, with whom he gets on well. He tends to be the more aggressive of the two, but not pathologically so. His I.Q. is 108.

Case 5

This baby was admitted to hospital in September, 1952, at the age of 11 months. He was born eight weeks prematurely and his head had always been thought to be a little large. Five weeks before admission he began to vomit frequently and his head grew rapidly. The skull circumference was 53 cm. and the fontanelles were wide and tense. Ventriculography showed a communicating hydrocephalus. The pallium measured 1 cm. anteriorly and 0.5 cm. posteriorly. After admission he had several attacks of opisthotonos and extensor rigidity. The operation of theco-peritoneal anastomosis was urgently carried out. After operation extensor rigidity of the lower limbs continued for three days and he then progressed normally. The skull circumference decreased by 1 cm. and the fontanelles closed. At 16 months he was trying to stand. Just before he was 2, his parents emigrated to New Zealand. He was not seen again until he was 5.

The history was then given that six months after arrival in New Zealand he developed a severe gastroenteritis, attributed by his parents to eating bad fruit. The following day he could not move his legs, showed complete loss of sensation below the umbilicus, and was incontinent of urine and faeces. Presumably he had some form of myelitis. According to his father the condition continued unchanged for two years—he was then 4. Bladder and bowel control then returned, followed by restoration of sensation and the development of spasticity and some movement in the legs. He returned to Ireland in 1956. There was no evidence that he had ever developed pressure sores, his sphincters were competent, and he had a spastic paraparesis. The beginning of his schooling was delayed because of his difficulty in walking and his parents' natural unwillingness to send him to a residential institution for cripples. He began home tuition at the age of 5½ and went to school when he was 6.

This child has had a great deal of care from very devoted parents, but he is not spoilt. He has an elder brother eight years older, and they get on well together. He tends to ignore his disability and does not like to be treated differently from "normal" children. He is happy at school, where his reports indicate his attainments to be slightly above average and his personality pleasing. His I.Q. is 110.

Clinical Summary

This group, small though it is, presents an interesting cross-section of treated hydrocephalic infants of the "infantile" or idiopathic type (idiopathic because it is still undetermined whether the cause is overproduction or under-absorption of C.S.F.). It may be that these are all cases of tentorial or cisternal obstruction (Laurence, 1959), but the evidence of air pictures taken in 1952 is not conclusive enough to be dogmatic on this point. They presented at ages varying from 1 week to 11 months. They all had grossly expanded brains, but only the two children with spastic legs and nystagmus respectively had any neurologically detectable lesion. One child had to be operated on twice in the first month, and one required a second drainage-tube when he outgrew his first. The latter also fractured his second tube over a rib margin. One developed a permanent nystagmus, two alternating squints, and one a sixth-nerve palsy. One developed epilepsy. The well-known complications of subdural haemorrhage and meningitis were represented in the non-surviving members of the group. One developed what must be a very rare type of localized spinal meningitis or myelitis from a bowel infection—the infection presumably travelling along the polythene tube.

In spite of their many adventures, all the survivors have reached school age with I.Q.s just over 100—this figure is regarded as purely coincidental in a small series—showing no obvious personality disorders and apparently happily integrated into their families. The prognosis for adult life is still uncertain, but a fairly hopeful one seems to be justified.

Discussion

Information on the long-term follow-up of operations for hydrocephalus is scanty. Scarff (1959) has followed up two series of cases treated personally by endoscopic cauterization of the choroid plexus, a method which no

longer enjoys great popularity. Five of the first series of 20 are alive, 17 to 19 years after operation, two of whom are of subnormal intelligence. Thirteen of the second series of 19 are alive 9 to 11 years after operation. Five are severe mental defectives, three are moderately retarded, and five are of normal intellect. Jackson and Snodgrass (1955) followed 62 patients operated on in a four-year period. Only four had drainage-tubes for more than three years, and, of these, only one had infantile hydrocephalus. About 40% of these patients were benefited for over two years, and the authors think that the longer the patients are followed the worse will be the results. This is not in agreement with the experience in this centre, where most of the failures have occurred in the early post-operative months. Of those surviving over two years, only one has had to be operated on again, and that successfully.

It seems likely that only a small percentage of these infants continue to require drainage for ever, because a tube allowing only 2 in. (5 cm.) for growth at either end at the time of its insertion is outgrown some time in the child's third year. What is required of the operation is to supply a safety-valve which will function efficiently for two years. At some time during this period balance between fluid production and absorption will probably be achieved. This is a speculative working hypothesis for use until the pathology of communicating hydrocephalus is understood. The common diagnosis may be cisternal obstruction as mentioned above.

This paper helps only in a negative way in the choosing of patients for operation. It has been suggested that if less than 2 cm. of pallium remains, as judged by ventriculography, operation is not worth while (Scarff, 1952). Only one of the infants described here had a brain thickness of more than 1 cm., and in two it was about 0.5 cm. We have not had cause to regret operating on these children. If there is any criterion for selection it is not pallial thickness. If there is no clinical evidence of gross cerebral damage, and there seldom is, selection should probably be by distillation of the combined experience of the attending paediatricians and neurological surgeons. There is at present no single clinical or laboratory criterion of operability. Babies who "don't look as if they would do well" probably should not be operated on, but these are in a small minority. Most infants with communicating hydrocephalus look well unless they have been vomiting over a long period. Babies with associated myeloceles or aqueduct stenosis or who have developed obstructive hydrocephalus after meningitis or neonatal haemorrhage, are a different matter, and the operability in each case must be decided on its merits.

At the beginning of this paper it was said that Laurence's (1958) figures for untreated hydrocephalics of mixed aetiology raised the whole question of the surgical treatment of this disorder. If his figures are broken down, it is found that, out of 182, 46% survived, 30% had I.Q.s of over 50 and were presumed educable, and only 6.5% had I.Q.s over 100. In so far as the present small series gives any guide to surgical treatment, it would suggest that the cisternal obstruction or communicating group should almost always be treated surgically and that the outcome is likely to be favourable if the early complications of operation are avoided.

Summary

A follow-up study has been made of five children surviving out of eight operated on for communicating hydrocephalus in 1952. Their physical, emotional, and intellectual status was reviewed and found to lie within the normal range.

The aim of operation for communicating hydrocephalus is discussed. If the early complications of operation are avoided and the infant is protected against high intracranial pressure for about two to three years the prognosis for normal survival appears to be good. There is still no definite criterion of operability. Thickness of surviving brain is not a reliable prognostic guide to the intellectual or emotional status of the survivors.

We are grateful to Professor F. M. B. Allen and other paediatricians in Belfast who referred these patients and helped in their care; to Dr. W. H. T. Shepherd, who did the ventricular studies; and to Mr. R. G. Woods, who took the photographs.

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SEMINAL ANALYSIS IN 22 HOMOSEXUALS

BY

DENIS PARR,* M.D., D.P.M.

Lately Research Fellow, St. George's Hospital, London; Senior Psychiatric Assistant, London Hospital

AND

G. I. M. SWYER, D.M., M.D., D.Phil., M.R.C.P.

Consultant Endocrinologist, Department of Obstetrics and Gynaecology, University College Hospital, London

The concept of male homosexuality as a form of constitutional deviation has given rise to a variety of somatic, anthropometric, and genetical studies directed to the discovery of physical correlates of the deviation. Particular attention has been paid to body build, hormone balance, and the structure of cell nuclei, but little work has been done on primary gonadal function in this connexion. Raboch and Nedoma (1958) reported that of 194 homosexuals examined at the Sexological Institute, Prague, only nine had hypoplastic testes (measuring less than 3.4 cm. in the long axis). We have been unable to trace any reference to seminological studies in homosexuals. It is well known that homosexuals who marry often prove themselves fertile, but they may be unrepresentative of homosexuals as a whole: for example, a much higher proportion of the married group may be bisexual.

To test the hypothesis that homosexuality is correlated with testicular inadequacy, seminal analysis was carried out in 22 homosexual men of whom 20 were single and none had more than a very small conscious heterosexual component in his make-up.

*Now Consultant Psychiatrist, Roffey Park Rehabilitation Centre, Horsham, Sussex.

Method

Patients for this study were derived from two sources: 13 were seen by one of us as psychiatric out-patients (12 at hospital and one privately) undergoing clinical investigation and treatment, and nine were referred by Mr. Gordon Westwood from his research series of male homosexuals belonging to a normal—that is, non-penal and non-psychiatric—population. The criteria of selection were (*a*) exclusive or very predominant homosexuality (all but two rating 5 or 6 on the Kinsey scale), and (*b*) readiness to take a seminal specimen to University College Hospital for testing after a minimum of three days' continence. Although anonymity was assured by the use of code numbers instead of names, a large (unrecorded) number of men who were asked to take part declined to do so because of the inconvenience involved, and the series represents only a minority of those approached. One case (No. 13) was tested elsewhere.

Findings

In the accompanying Table the following items are included:

Age.—Range 18–56; mean 29.8; median 28.

Marital Status.—20 single, 1 married, 1 previously married.

Kinsey Rating.—Subjects were rated on the 7-point Kinsey scale of heterosexuality–homosexuality, ratings 4, 5, and 6 having the following meanings: 4, predominantly homosexual in activity and/or psychic reactions; 5, almost exclusively homosexual in orientation; and 6, exclusively homosexual in orientation.

Details of Cases

Case No.	Age	Marital Status	Clinical					Seminal Analysis				
			Kinsey Rating	Homosexual Experience	Heterosexual Experience	Active or Passive	Effeminate Manners	Volume (ml.)	Density (millions/ml.)	% Abnormal Forms	Motility	Fertility Rating
Psychiatric												
1	23	S	6	+	+	–	±	3·7	27	25	G	B
2	35	M	5	+	+	P	±	1·7	144	23	G	HF
3	26	S	6	+	0	A	0	3·7	50	23	M	B
4	56	(M)	6	+	+	P	+	0·9	195	22	G	HF
5	28	S	6	+	0	P	+	1·5	76	12	G	HF
6	18	S	5	+	0	–	+	1·8	52	30	G	F
7	22	S	6	0	0	–	±	4·0	115	28	G	HF
8	48	S	5	+	0	–	0	2·6	50	16	G	F
9	33	S	5	+	+	–	0	2·6	66	26	G	HF
10	28	S	4	+	0	–	0	4·0	125	18	G	HF
11	27	S	5	+	0	–	0	4·3	60	33	M	F
12	29	S	6	+	0	P	+	3·0	41	46	P	B
13	33	S	5	+	+	–	0	5·0	95	?	?	HF
Non-psychiatric												
14	38	S	6	+	0	–	0	3·7	55	18	P	B
15	33	S	5	+	0	A	0	3·0	1	—	P	S
16	27	S	6	+	0	A	0	2·4	65	27	G	HF
17	33	S	6	+	0	–	0	2·4	1	—	Nil	S
18	22	S	5	+	0	–	±	2·0	16	13	G	SubF
19	23	S	5	+	0	P	±	1·5	39	26	P	SubF
20	29	S	4	+	+	A	0	3·2	24	15	G	B
21	29	S	6	+	+	P	0	4·3	46	16	G	F
22	25	S	6	+	0	–	0	2·3	10	20	G	SubF

Homosexual Experience and Heterosexual Experience.—These items refer to the history of acts with others at genital level. 21 had had homosexual experience, 7 heterosexual experience.

Active or Passive.—A pronounced preference for one or other role is shown by A (4 cases) or P (6 cases).

Effeminate Manners.—The presence in marked or slight degree of effeminate ("pansy") mannerisms is shown in the Table by a + or ± sign respectively, while their absence is denoted by a 0 sign.

Other Clinical Features.—Three patients (Cases 4, 5, and 12) had trans-sexualist desires—that is, wanted to change sex and to have surgical treatment to this end. One of these (Case 4) had twice, and very briefly, been married for reasons of expediency unconnected with his sex life. Case 6 was a dullard whose general development was immature—that is, he looked and acted much younger than his years—although his genitalia were normal. Case 9, unlike other members of this series, was paedophilic (had impulses directed towards boys). There was no history of genital maldevelopment or damage in Cases 1 to 13, but in Mr. Westwood's series (Cases 14 to 22) no special inquiry had been made about past physical health. Cases 15 and 17, but not the other members of the latter series, agreed, on being told of the abnormal seminal findings, to see one of us, and they then gave histories of an operation for cryptorchidism at the age of 9 (Case 15) and of bilateral orchitis at 20 (Case 17).

Seminal Analysis.—The volume, sperm density, and percentage of abnormal forms are tabulated. In addition, the following ratings have been made:—*Motility*: G=Good. M=Moderate. P=Poor. *Fertility*: HF=Highly fertile. F=Fertile. B=Borderline. SubF=Subfertile. S=Sterile.

Nuclear sexing was carried out at St. George's Hospital on blood smears by Dr. J. L. Stafford and his colleagues in Cases 3, 5, 6, 7, 8, 12, 15, and 17, and the cytological appearances were found to be within the normal limits for genetic males in each case.

Discussion

On the basis of the seminal findings in this group of patients, it may be concluded that two are virtually sterile (due to cryptorchidism and to post-pubertal orchitis respectively); three are subfertile, with sperm counts of 10, 16, and 39 millions per ml., spermatozoal activity being poor in the last case; five are of borderline fertility, with sperm counts of 24–55 millions per ml., but those with the higher counts showing poor spermatozoal activity; four are of normal fertility, with sperm counts of 46–60 millions per ml. with good activity; and eight are highly fertile with sperm counts of 65–144 millions per ml. with good activity.

For comparison, taking into account sperm counts only, 1,000 men whose semen was examined in the Fertility Clinic at University College Hospital showed the following distribution: with azoospermia, 8.5%; with less than 20 millions per ml., 12%; with 20–49 millions per ml., 18.5%; with 50–100 millions per ml., 24%; with more than 100 millions per ml., 37%.

The numbers of cases in the present study are too small to break down in a comparable way, but if we group both series into less than 50 millions per ml. and more than 50 millions per ml., we obtain 39 and 61% for the 1,000 men and 41 and 59% for the present series. This suggests that the distribution of seminal analyses in this series is not different from that of the 1,000 men. Since those 1,000 men were husbands of couples complaining of infertility, it cannot be assumed that their seminal findings represent those of the population generally, though this is, in fact, probably not far from the truth. The basis for this statement is the belief, generally held, that approximately one-third of all men show some degree of subfertility.

However, there is a very striking difference between the psychiatric patients (Cases 1–13) in the series and

Mr. Westwood's subjects (Cases 14–22), who were not under psychiatric treatment. Thus, of the psychiatric group 11 out of 13 had sperm counts of 50 millions per ml. or more, while of the non-psychiatric group only two out of nine had counts over this level. There was little difference in volume, percentage of abnormal forms, or motility between the two groups, but differences in sperm density were reflected in an overall rating of "highly fertile" or "fertile" in 10 out of 13 psychiatric as against 2 out of 9 non-psychiatric cases.

Confirmation (from larger and more comprehensive surveys) of the striking difference in fertility between the two subgroups in our series would be of considerable importance in relation to theories of aetiology of homosexuality. Hypotheses readily come to mind in this context, but we think it inappropriate to list them at this stage in view of the small size of our study. The difference noted, if not fortuitous, may well be an artifact of the selection procedure. For example, some of the non-psychiatric subjects may have volunteered because they were already conscious or suspicious of genital abnormality, whereas psychiatric patients who chose to take part may have been influenced by quite different motives.

Summary

22 men who were predominantly or exclusively homosexual in orientation provided seminal specimens for analysis.

Of the 22, 8 were rated highly fertile, 4 fertile, 5 borderline, 3 subfertile, and 2 sterile, on the basis of the seminological findings.

The clinical diagnosis of "constitutional type" homosexuality was compatible with a high degree of fertility as judged seminologically.

The distribution of seminal analyses was similar in the group as a whole to that of a control group of 1,000 husbands of couples complaining of infertility.

Within the series there was a conspicuous difference between 13 patients under psychiatric treatment and 9 subjects drawn from a "normal" population. 10 out of 13 of the psychiatric, but 2 out of 9 of the non-psychiatric, group were rated as fertile or highly fertile. This is an interesting finding, but must be interpreted with great caution in view of the small size of the series and the method of selection.

We are indebted to Dr. J. L. Stafford and his colleagues and to Mr. Gordon Westwood for their collaboration. One of us (D. P.) acknowledges with thanks financial support from the Research Funds, St. George's Hospital.

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"Since the middle of the nineteenth century we have successfully dealt with most of the public-health problems associated with the early industrial revolution. Contaminated water supplies, non-existent or inadequate sewerage, bad housing are no longer the widespread health hazards they once were in our towns. But dirty air is one legacy of the past which is still very much with us, and is still a serious threat to health." (Sir KEITH JOSEPH, Parliamentary Secretary, Ministry of Housing and Local Government, at Harrogate Conference, National Society for Clean Air.)

LACTIC DEHYDROGENASE ACTIVITY IN ACUTE MYOCARDIAL INFARCTION

BY

J. KING, B.Sc., A.I.M.L.T.

Biochemist, Group Pathology Department, Barrow-in-Furness

AND

A. P. B. WAIND, D.S.C., M.D., M.R.C.P.

Consultant Physician, North Lonsdale Hospital, Barrow-in-Furness

The estimation of serum glutamic-oxalacetic transaminase (GO-T) has been used in the diagnosis of cardiac infarction since 1954 (LaDue *et al.*, 1954). Although this aid to diagnosis is now widely accepted, Dewar *et al.* (1958) have shown that false-negative results occur in 8.8% of cases. In those cases where the GO-T activity is raised, the increase is usually confined to a period of three to six days after the onset of pain (Wróblewski and LaDue, 1956).

The procedure for assay of serum GO-T activity by the techniques suited to routine work (Mohun and Cook, 1957; Reitman and Frankel, 1957; King, 1960a) is rather lengthy, and this fact, associated with the limitations previously mentioned, prompted an examination of the serum levels of other enzymes in cases of suspected cardiac infarction.

Hill and Levi (1954) demonstrated the presence of lactic dehydrogenase in human blood serum, and Wróblewski and LaDue (1955) observed an increase in activity similar to that of GO-T in cases of cardiac infarction. Wacker *et al.* (1956) confirmed this observation on 22 patients, as did Zimmerman and Weinstein (1956) on five patients in whom elevated enzyme activity up to two weeks after infarction was noted.

Snodgrass *et al.* (1959) repeated the work in great detail and showed in a large series of cases that cardiac infarction was invariably associated with elevation of lactic dehydrogenase level of serum. They considered such enzyme assay to be a determinate diagnostic measure in cardiac infarction.

Lactic dehydrogenase (LDH) is an enzyme, which, utilizing coenzyme 1 (DPN) as hydrogen carrier, shows its greatest activity in the reaction,

$$\text{lactate} + \text{DPN} \overset{\text{LDH}}{\rightleftharpoons} \text{pyruvate} + \text{DPNH}_2.$$

The present report deals with the serum levels of LDH compared with those of GO-T found in serial assays on a series of cases admitted to hospital with cardiac pain.

Methods and Materials

Serum GO-T was estimated by the method of King (1960a). LDH activity was assayed using a colorimetric technique. This technique and the values encountered in normal subjects have been described elsewhere (King, 1959, 1960b).

The clinical material consisted of 50 subjects admitted to the North Lonsdale Hospital with cardiac pain and electrocardiographic changes supporting a diagnosis of coronary thrombosis. Cases in which the electrocardiographic findings were equivocal, or were

obscured by previous infarction, or in which there was bundle-branch block, were excluded. Otherwise the series was a consecutive one. The ages of these subjects range from 38 to 76 years, and there were 12 females and 38 males. Blood specimens for enzyme estimation were obtained from the patients as soon as practicable after admission, and later specimens as required for prothrombin-time estimation in the control of anti-coagulant therapy, or periods of up to three weeks after admission to hospital. In all more than 900 assays were performed on the specimens received.

Results

The series was divided into two groups.

Group 1

This group consisted of 32 patients who we considered had had unequivocal myocardial infarction. The criteria for inclusion were that there should have been a history of typical prolonged cardiac pain and electrocardiographic changes of the Q and T type, characteristic of acute transmural infarction.

In 29 of these cases the serum GO-T level was elevated for a period of from three to nine days, with an average of five days. In three subjects no abnormal increase in GO-T activity was detected, but these subjects were late admissions. Specimens for assay were not received until four to seven days after the onset of pain, and it may have been that the rise and fall of GO-T activity occurred before admission.

In every one of the 32 cases in this group the serum LDH activity was raised. The period of elevation ranged from a minimum of six to a maximum of more than 14 days, with an average of 11 days. The elevation of serum LDH activity lasted longer than that of GO-T in every patient except for one, who died on the ninth day, in whom both serum enzyme activities were grossly raised after extension of the infarction. Table I shows ages and sexes of this group with comparisons of duration of LDH and GO-T activity in the individual cases. Fig. 1 shows the serial enzyme levels encountered in this group.

Group 2

This group comprised 18 patients who gave a typical history of prolonged cardiac pain but in whom the electrocardiograph showed only T-wave changes, sometimes transiently in serial records. These patients were placed in a separate group because some slight doubt existed about whether actual muscle death had occurred. This group contained 4 females and 14 males aged from 46 to 71 years.

Serum LDH was elevated in all but two of these subjects, and, in one of those, specimens for assay were not received until eight days after the presumed date of infarction. In the other case, however, specimens were received on the same day as the onset of pain. Serum GO-T showed no increase in activity in these cases or in a further three from whom specimens were received after two, five, and six days respectively. Table II and Fig. 2 summarize these results.

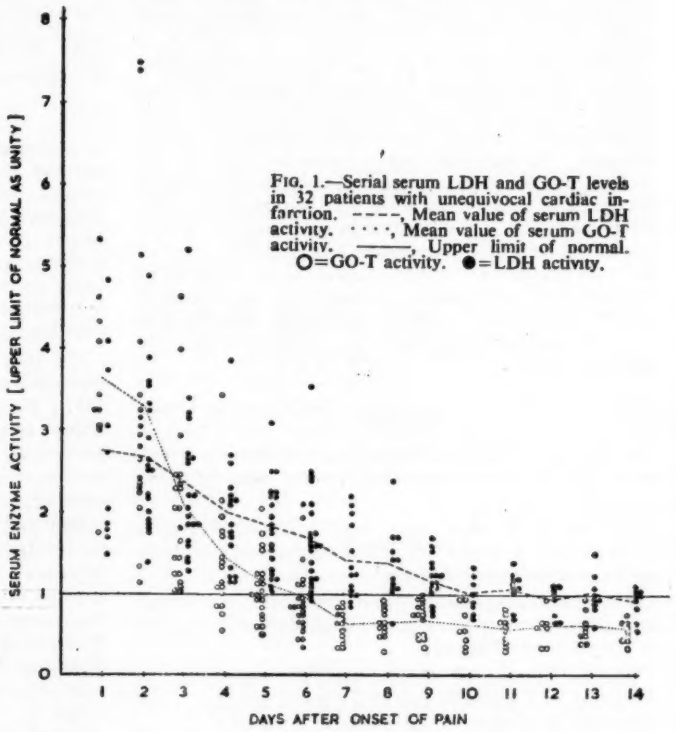

FIG. 1.—Serial serum LDH and GO-T levels in 32 patients with unequivocal cardiac infarction. ----, Mean value of serum LDH activity. ····, Mean value of serum GO-T activity. ——, Upper limit of normal. O=GO-T activity. ●=LDH activity.

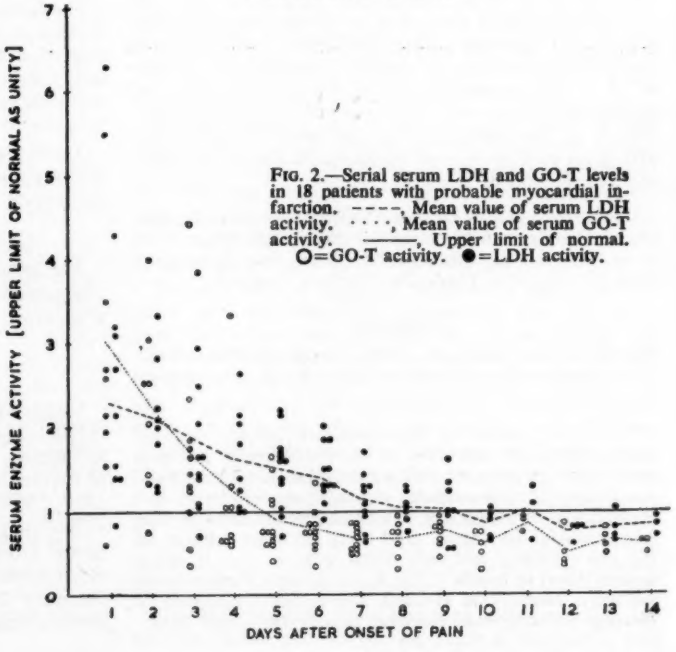

FIG. 2.—Serial serum LDH and GO-T levels in 18 patients with probable myocardial infarction. ----, Mean value of serum LDH activity. ····, Mean value of serum GO-T activity. ——, Upper limit of normal. O=GO-T activity. ●=LDH activity.

Discussion

A comparison between the clinical value of these two enzymes, based on the series of cases investigated, shows that LDH assay is at least as sensitive as that of GO-T. The group of 32 cases of undoubted infarction which produced 100% positive results using the LDH test is especially significant in this regard. In the whole series LDH assay yielded negative results in only two cases, one of which was a late admission to hospital. It would seem that LDH elevation occurs almost invariably at some period during the first 14 days after cardiac infarction, and in this regard our results are in keeping with those reported by Snodgrass *et al.* (1959). Serum GO-T activity, on the other hand, was normal in these two cases mentioned and in a further six subjects.

TABLE I.—*Serum GO-T and LDH Activity in* 32 *Patients with Electrocardiographic Evidence of Myocardial Infarction*

Case No.	Sex and Age	Day First Specimen Received	Duration of GO-T Elevation	Duration of LDH Elevation
1	M 56	1	5	14
2	F 60	1	5	10
3	F 67	4	<4	11
4	M 59	2	8	Till death on 11th day
5	M 64	1	4	8
6	M 55	1	5	13
7	M 41	2	4	7
8	F 76	2	5	9
9	F 70	2	4	6
10	M 55	1	4	10
11	F 72	5	5	12
12	M 53	3	5	12
13	M 46	3	3	10
14	M 65	1	5	12
15	F 71	2	5	13
16	M 38	2	5	14
17	M 68	1	7	14
18	M 55	3	6	11
19	M 54	1	6	12
20	M 48	4	5	11
21	M 57	2	3	7
22	M 57	3	Till death on 9th day	
23	M 52	1	5	8
24	F 53	7	<7	14
25	F 68	3	5	10
26	M 64	3	4	6
27	M 60	5	<5	14
28	M 55	1	4	8
29	M 51	2	5	8
30	M 53	2	5	9
31	M 54	6	6	11
32	M 68	2	3	10

The elevation of serum LDH activity was always prolonged beyond that of GO-T, and this might well be useful in the investigation of cases of myocardial infarction admitted late to hospital. The scattergrams demonstrate this point. They also show that GO-T is relatively more elevated during the 48 hours after infarction, while after this interval LDH is the more sensitive index.

TABLE II.—*Serum GO-T and LDH Activity in* 18 *Patients with Probable Myocardial Infarction*

Case No.	Sex and Age	Day First Specimen Received	Duration of GO-T Elevation	Duration of LDH Elevation
1	M 71	3	5	11
2	M 60	2	4	10
3	M 62	1	4	8
4	M 60	5	<5	9
5	M 69	6	<6	13
6	M 69	8	<8	<8
7	M 59	2	5	9
8	F 58	1	Till death on 5th day	
9	M 69	1	3	7
10	M 64	2	4	8
11	M 60	1	3	5
12	M 49	1	3	6
13	F 46	1	4	6
14	F 67	2	4	10
15	M 59	1	None	None
16	M 53	1	6	>9
17	F 61	1	5	11
18	M 65	2	<2	4

From a laboratory point of view LDH estimation is simpler to carry out than that of GO-T whatever the method used, and, taking less time, represents a considerable saving in laboratory resources.

Serum LDH elevations have been noted in various other disease states (Hsieh and Blumenthal, 1956), particularly in carcinoma (West and Zimmerman, 1958), anaemia (Zimmerman *et al.*, 1958), and leukaemia (Blanchaer *et al.*, 1958). We have also observed rises in mitral stenosis with heart failure, femoral-vein thrombosis with oedema, pneumonia, and cerebral thrombosis.

This formidable list would lend itself to endless false-positive results if it were suggested that estimation of LDH activity was a specific test for cardiac infarction. However, in its correct clinical setting—that is, in the investigation of cases of chest pain of cardiac type—the assay appears to have considerable value and certain advantages over enzyme assays at present accepted as useful.

Summary

A comparison is made between the serum lactic dehydrogenase and glutamic-oxalacetic transaminase activities in a series of 50 cases of cardiac infarction.

The advantages of the former assay in the investigation of this condition are discussed.

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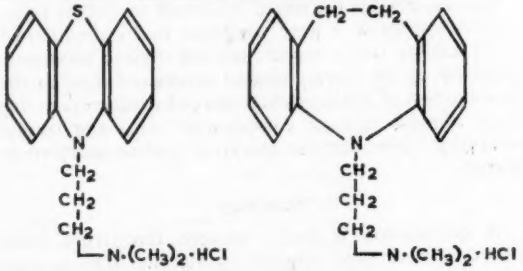
A new monthly publication, *Abstracts of Japanese Medicine*, is now being published by the Excerpta Medica Foundation with the aid of a grant from the Public Health Service, National Institutes of Health, U.S. Department of Health, Education, and Welfare. The chairman of the Japanese editorial board is Professor T. YOSHIDA, dean of the faculty of medicine, University of Tokyo. The publication includes a list, translated into English, of the periodicals covered and indicates those which are published in the English language. Details may be obtained from the Excerpta Medica Foundation, 119–23 Herengracht, Amsterdam-C., The Netherlands, or 56 Grosvenor Hill, Mayfair, London W.1.

Medical Memoranda

Hypothermia Induced in a Myxoedematous Patient by Imipramine Hydrochloride

The "cooling" effect of the phenothiazines, particularly chlorpromazine, is well known (Courvoisier *et al.*, 1953). Mitchell *et al.* (1959) have shown that chlorpromazine can precipitate a hypothermic myxoedema coma in a hypothyroid patient. A similar pharmacological action would not be surprising from chlorpromazine and imipramine hydrochloride ("tofranil") owing to the close structural similarity of these two agents:



CHLORPROMAZINE IMIPRAMINE HYDROCHLORIDE

Sigg (1959) showed, however, that the cooling effect of imipramine on experimental animals was much less than that of chlorpromazine.

Case Report

A widow aged 57, with suspected myxoedema since childhood, was admitted to the psychiatric unit because she had been expressing paranoid ideas against her neighbours, and was in a state of extreme neglect. Since childhood she had received only sporadic thyroid replacement therapy, and in fact no thyroid or equivalent had been taken for the last 10 years.

Physical examination revealed a thin, anaemic woman 4 ft. 5 in. (134.5 cm.) tall, weighing 82 lb. (37.2 kg.). The scalp hair was coarse and was falling out on the occipital region, but her eyebrows were bushy. The skin was dry and rough. Her voice had the typical fruity, croaking quality of myxoedema. Temperature on admission was 97.4° F. (36.3° C.), pulse 76, and B.P. 150/90.

Associated with the signs of myxoedema were definite traits of mongolism such as short fingers, the fifth turning markedly inwards, and prominent transverse palmar creases. The epicanthic folds were not pronounced, but the bridge of the nose showed marked flattening. No abnormal signs were detected in the other systems.

Her paranoid ideas disappeared without specific treatment, and she entered into the activities of the ward. Her intelligence was that of a high-grade mental defective. During this period of improvement she fell on the ward floor, sustaining a haematoma of the occipital region. She was confined to bed and became drowsy, though capable of being roused and of eating. No new abnormal signs were detected in the nervous system, and *x*-ray examination of the skull showed no fracture. She remained apathetic, depressed, and was easily moved to tears; consequently a course of imipramine was given. After two days' treatment a consistently low temperature was recorded. The patient was in a pre-comatose state, and could be roused only with difficulty; feeding was impossible.

Investigations.—Hb, 52.5%; W.B.C., 5,600/c.mm., with normal differential count; blood cholesterol, 190 mg./100 ml.; fasting blood sugar, 107 mg./100 ml.; blood urea, 104 mg./100 ml. Electrolytes (mEq/l.): Na 125, Cl 107, K 4.1. CO_2 combining power, 20.4. Plasma proteins, 6.5 g./100 ml. E.C.G.: sinus tachycardia, low-voltage complexes, and flat T waves. The Wassermann reaction was negative.

The temperature, recorded by a full-scale thermometer, was 93° F. (33.9° C.) after a total dosage of 200 mg. of imipramine. The drug was stopped immediately and her

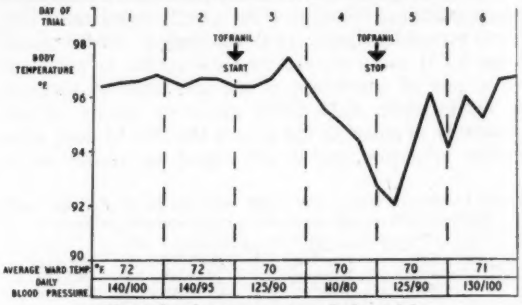


Chart showing temperature during trial.

temperature rose to 98° F. (36.7° C.) in 24 hours. The hypothermic episode was thought to be due to the imipramine, but other factors such as ward temperature had not been recorded during the episode. A further course of imipramine was therefore given, and the patient's rectal temperature was recorded four-hourly with the ward temperature. The Chart shows the temperature curve 24 hours before imipramine was given and while the drug was administered, hypothermia being observed 48 hours after starting the second administration. At no stage did we observe the excessive sweating sometimes attributable to this drug.

The onset of hypothermia was similar in both attempts to use imipramine; the rise in temperature after the second attempt, however, was protracted and erratic. L-Thyroxine was given immediately; since then her progress has been uneventful.

Comment

As chlorpromazine is capable of inducing a hypothermic coma in myxoedematous patients, it was possible that a similar drug, such as imiprazine hydrochloride, could also induce hypothermic coma. No such experience has yet been recorded. The patient reported here would undoubtedly have sunk into deep coma if she had not been observed carefully and the drug withdrawn promptly. Furthermore, the dose of the drug had not been excessive (100 mg. daily). The speed with which the temperature was lowered is alarming when one considers that the patient was in bed continuously in a warm ward (70° F.; 21.1° C.).

Drugs of the phenothiazine group and related substances are often prescribed for patients who are not under continual observation, and it is felt that caution is needed, particularly in the presence of hypothyroidism, if serious and often fatal calamities due to hypothermic coma are to be avoided.

We thank Dr. M. R. Leaby for permission to study his patient and to prepare this report, and Mr. F. J. N. Powell for the biochemical estimations.

M. D. McGrath, M.B., Ch.B.,
Registrar.
R. G. Paley,* M.D., Ph.D., M.R.C.P.Ed.,
Late Assistant Physician.
St. James's Hospital, Leeds 9.

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*Now at Preston Hospital, North Shields.

Reviews

DEVELOPMENT OF THE YOUNG CHILD

The Development of the Infant and Young Child: Normal and Abnormal. By R. S. Illingworth, M D.Leeds, F.R.C.P., D.P.H., D.C.H. (Pp. 318+viii; illustrated. 27s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

This is a thoroughly excellent book and should be read by everyone who may be called upon to assess infants' and young children's mental development; many will be glad to have it at hand for reference. The author's early training in Gesell's clinic is evident and has borne abundant fruit, for he is now an acknowledged expert in his own right, and this book contains many of his original ideas. It is clearly written and the book is well produced. There are 95 illustrations: those of "a normal premature baby" and "an untreated cretin" are not particularly happy choices, nor is the "method of testing the knee-jerk" in which the tester's hand, wristwatch, ring, and large patellar-hammer predominate—an unnecessary illustration in any case. On the other hand the series of photographs (6–47) depicting the stages of development are wholly delightful.

The chapter on the association of physical defects and of disease with mental development is perhaps the least good, consisting as it does for the most part of a collection of rare disorders in which varying degrees of mental defect may or may not occur. Professor Illingworth is more at home when he is quoting from his own experience. The last chapter, on mistakes and difficulties in developmental diagnosis, is extremely valuable, but so indeed are most of the others, particularly those on variations in individual fields and in the pattern of general development. A lighter note is introduced by a short and amusing chapter on mental superiority. The summaries at the end of the chapters are helpful, and there is a good bibliography.

WILFRID GAISFORD.

THE LEUKAEMIAS

Leukaemia. Research and Clinical Practice. By F. G. J. Hayhoe, M.A., M.D.(Cantab.), M.R.C.P.(Lond.). (Pp. 335 +viii; illustrated. 80s.) London: J. and A. Churchill, Ltd. 1960.

It is curious that for twenty years after the publication of Forkner's monograph on leukaemia and allied disorders no other book appeared in the English language on this disease, and now two have been published in quick succession. We have already reviewed Dameshek and Gunz's *Leukemia* and can begin this review by saying that there is no clash between this book and Hayhoe's *Leukaemia*, as the two approaches to the subject are different. Hayhoe's theme is outlined in his subtitle, Research and Clinical Practice, and it is his critical discussion of research on leukaemia during the last two decades that makes this such a valuable book. The first two-thirds of the text are devoted to an exposition of basic knowledge of the aetiology, pathology, and therapy of leukaemia, leaving the final third for the clinical features.

The book begins with an account of recent work on the incidence, aetiology, and transmission of leukaemia. There is then an extremely valuable account of the leukaemic cell. The author has himself been especially interested in cytochemical studies of leukaemia, and these are described with a wealth of illustration. The aim of such studies is, first, to see whether there is any absolute difference between leukaemic and normal cells, and to this the answer is no; and, secondly, to improve our ability to differentiate the various types of acute leukaemia. Hayhoe has summarized the staining characteristics of the different leukaemias in his Table IV, which will be of great value to haematologists and clinical pathologists. It would be interesting to see a formal comparison between these rather time-consuming histochemical techniques and phase-contrast microscopy in the differentiation of the acute leukaemias.

The general principles of therapy of the leukaemias are next considered, and the discussions on the general effects of irradiation of the spleen, and on the treatment of leukaemia by massive irradiation and transfusion of bone-marrow, are of special interest. Hayhoe makes the point that average figures for duration of life in acute leukaemia are of little value in giving a prognosis in the individual case, where the all-important question is whether the cells are or are not resistant to therapy. The final section of the book describes the clinical features of the leukaemias. Some of the sections, such as those on eosinophilic leukaemia and systemic mastocytosis, will be of special interest to the more advanced student.

The book is lucidly written and there are extensive lists of references. It is both scholarly and practical. It is printed on a large page which is easy to read and which is a good size for the plates, and the illustrations, both coloured and black-and-white, are excellent. The book will enhance the reputation of British haematology.

L. J. WITTS.

HEALTH SERVICES

Health Service, Society, and Medicine. Present Day Health Services in Their Relation to Medical Science and Social Structures. By Karl Evang, M.D. *University of London Heath Clark Lectures, 1958.* (Pp. 171+viii. 21s.) London, New York, Toronto: Oxford University Press. 1960.

The Heath Clark Lectures for 1958 well deserve publication in book form; not only because they express the considered opinions of a man who, after seven years in general practice, became Director-General of Health Services in Norway with exceptional opportunities to observe developments in other countries, but also because they have historical value in their careful description of a particular phase in the evolution of medical practice.

The idea that health services should be deliberately organized by society in its own interest is not new. Sir Thomas More discussed it in his *Utopia* more than four hundred years ago, but little could be done without exact knowledge of the causes of sickness and until money could be found to meet the cost. Within the past hundred years all developed and wealthy communities have established health services, and it is not surprising that conceptions of their proper organization should vary, for these services are but one part of the social and administrative structure of a nation and reflect its culture.

Dr. Evang reviews the four main types existing to-day: the Western European, the chief defect of which is the separation of preventive and curative medicine; the American, which reflects the predominance of a free-for-all, competitive ideal and includes "greater diversities and inner contradictions than any other"; the Soviet system, which assumes full and undivided public

responsibility for the health service and so makes any form of insurance superfluous; and, lastly, the diverse, *ad hoc* programmes of underdeveloped countries.

The rapid progress of scientific medicine has convinced Dr. Evang that in future the role of a well-equipped hospital will be of paramount importance. Unexpectedly, but perhaps with truth, he pays tribute to the flexibility of hospitals, which have adapted themselves better to rapid change than general practice or the public health service. He points out that, despite the increased complexity of their work, they have managed to treat ever larger numbers of patients, and many of them have also established effective organizations for aftercare. About general practice he is a little worried; in his view the importance of the free, independent, and individualistic G.P. has been overstressed (he has become "the sacred cow of professional associations in many countries") and while the value of the doctor-patient relationship is admitted Dr. Evang considers that in future it must have a firmer basis than the traditional one.

Other lectures deal with drugs and particularly with narcomania—to this writer a new but expressive term—and with the difficulties of the public health service "proper" as it would have been called less than twenty years ago.

A. P. THOMSON.

DIAGNOSING GROWTH

Growth Diagnosis. Selected Methods for Interpreting and Predicting Physical Development from One Year to Maturity. By Leona M. Bayer and Nancy Bayley. (Pp. 241+xiv; illustrated. 80s.) Chicago: University of Chicago Press. London: Oxford University Press. 1959.

In this interesting monograph the authors, both of whom are well known in the United States for their part in growth studies, discuss selected methods of interpreting and predicting human development from the age of 1 year to maturity. In the first part they describe the methods of their choice—inspection, anthropometry, photography, and *x*-ray of the hand and wrist for skeletal age. From this they go on to the complicated task of interpreting growth trends using both distance and increment curves for height, weight, and three other measurements—biacromial and bicristal diameters and trunk length. In the second part they give full details of the growth of eight normal children, covering individual boys and girls maturing at the usual rate, unusually early, or late. They also illustrate the kind of transient obesity that may occur. The final sequence is of fourteen cases showing giantism, dwarfism, precocious menarche, obesity in boys, growth in adolescent girls following the rare trauma of castration, a hypogonadal boy, and female pseudohermaphrodism.

Carefully collected longitudinal data of this kind is of great value, because reliable information covering so many years is hard to come by. The actual numbers dealt with may be small, but the authors show how the problem of growth diagnosis may be tackled.

There are several criticisms. The bibliography is short and not up to date—there is no mention, for example, of recent contributions from this country. And if only three physical measurements are to be recommended to physicians on the grounds of time, no adequate explanation is offered for the authors' particular choice. Lastly, there is inconsistency in outlook concerning the limits of normal variation. Statements such as the following occur only too frequently in the text: "Absolute parameters are all *too* large, except for an average shoulder breadth." This is out of keeping with the author's excellent quotation from Gallagher and Gallagher: "It is as difficult as it is desirable to promote the idea of the importance of the individual in people whose world, while protesting a belief in freedom, bombards them with talk about average size, behaviour and attitudes."

R. W. PARNELL.

ARTERIAL SUBSTITUTES

Autogenous Vein Grafts and Related Aspects of Peripheral Arterial Disease. By W. Andrew Dale, M.D. Preface by Earle B. Mahoney, M.D. (Pp. 123+xiii; illustrated. 48s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

A very large variety of materials have been used as arterial substitutes. For the replacement of the aorta many materials work well: the problem has been to find the best material to replace smaller vessels. Autogenous vein grafts were used in clinical practice before the first world war; they then were used sporadically until the recent development of other materials for arterial replacement rekindled interest in this whole subject. At first these newer materials were acclaimed as being better than autogenous vein grafts, but gradually those with experience in this field have been forced to eat their words and admit that vein grafts are in certain situations the best arterial substitutes.

The author of this monograph, Dr. W. A. Dale, has been a leader amongst the few champions of vein grafts whose faith was not shaken by the greater availability of other materials. He gives us in this book his experience with these and other types of arterial substitutes both in the experimental laboratory and in clinical practice. The result is a book which can be strongly recommended to those interested in arterial reconstruction.

CHARLES ROB.

CHEST AND HEART DISEASES

Diseases of the Chest Including the Heart. Edited by J. Arthur Myers, Ph.D., M.D. With 34 contributors. (Pp. 1,015+x; illustrated. £13 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

It is a little difficult to decide for whom this book is intended. Possibly it is intended for trainees in a specialty of cardio-respiratory disease which may exist on the other side of the Atlantic, but not in this country. It suffers from the usual defects of a book of multiple authorship, in that the individual contributions vary not only in their quality but also in the standard of reader to whom they appear to be directed; and, indeed, some of the contributions are written at no more than undergraduate level.

The balance of emphasis, as shown by the space devoted to various contributions, seems rather odd. The whole of tuberculosis is discussed in 46 pages—of which 13 are devoted to chronic pulmonary tuberculosis—out of the 595 pages in the part of the book dealing with diseases of the chest. It is difficult to believe that even in the most favoured areas the clinical importance of tuberculosis has diminished to such a degree as to justify such summary treatment. Certainly for physicians practising in most parts of the world this

section will seem far too brief in relation to the practical importance of its subject. Some technical aspects of heart surgery are dealt with authoritatively in 48 pages by Dr. Lillehei and Dr. Varco, but the surgery of the lungs is given no special attention whatever. There are many statements with which most physicians on this side of the Atlantic would disagree. For instance, emphysema is stated to be the most frequent complication of allergic bronchial asthma. Artificial pneumothorax is advocated as treatment for pulmonary tuberculosis, while the details of antibacterial treatment and the important problem of drug resistance are, to British eyes, very sketchily presented. Elsewhere what appear to us to be curious omissions are evident. The pneumoconioses are briefly dealt with under the general heading "air contaminants," and in the course of this article coal miners are not mentioned at all. There are some excellent sections dealing briefly with special topics. Notable among these are Dr. Boyden's on the segmental anatomy of the lungs, Dr. David Smith's on the pulmonary mycoses, and Dr. Bernard Lewis's on emotions and the circulation.

So far as the book as a whole is concerned, it seems to offer nothing that cannot be obtained as well, and for most purposes better, from other writings of some of the authors and from existing textbooks of cardiology and respiratory disease.

J. G. SCADDING.

GENETICS FOR EVERYMAN

Outline of Human Genetics. By L. S. Penrose, M.A., M.D., F.R.S. (Pp. 146+xii; illustrated. 12s. 6d.) London, Melbourne, Toronto: Heinemann. 1959.

It is most uncommon for a physician to be so gifted mathematically that he can understand all the intricacies of modern genetics, and an even more unusual combination is that being so endowed he can retain the capacity to explain a complicated, though not inherently difficult, subject to that overworked abstraction the "informed layman." Yet this is what Professor Penrose has succeeded in doing, and his book is also ideal for medical students because, being a medical man, he not only understands human genetics but also human beings.

Any student embarking on this book can be assured that it is assumed that he knows no genetics and possesses only the mathematical knowledge required by the General Certificate of Education. Furthermore, he will find that the subject matter does not become increasingly difficult as is the case with so many books on scientific subjects written for the general public.

Penrose begins with a chapter on basic observations in which he discusses the difference between segregating and non-segregating characters, the former (like achondroplasia) being inherited in an all-or-none manner and the latter (like height or weight) being a matter of quantitative difference. Because the segregating traits are usually controlled by a single gene they are easier to understand and the various methods of single-gene inheritance are discussed in considerable detail. On the other hand, the non-segregating traits for which many genes are responsible and where the answers are less clear-cut, are mentioned only in a general way.

Turning to genes and population, Penrose explains the fallacy in the common idea that because a gene is dominant it must necessarily spread. This leads on to a discussion of the idea of gene frequency and the Hardy-Weinberg formula showing how with random mating the genetical structure of a population remains the same. The diagrammatic explanation of the Hardy-Weinberg law is excellent, and no one after reading it should be in any doubt as to why the heterozygous "carrier" may be quite common even though one homozygote is extremely rare.

Associations and linkage are dealt with in an orthodox manner, but he is controversial in his last chapter on eugenics and dysgenics. He does not make it clear that the biological variability desirable in a population refers to "normal" characters and not to the pathological conditions which form the subject of so great a part of his book. Furthermore, his conclusions that "the genetical backbone of the population is, in fact, the despised mentally inferior tenth" (p. 118) seems unconvincing, because neither fertility nor intelligence can be accounted for on a single gene hypothesis which is his admittedly over-simplified model for these characters.

In spite of these minor criticisms the book has the overriding merits of being interesting, entirely comprehensible, and short. Such a combination is bound to appeal to medical students and anyone else who wishes to know the elementary facts about a rapidly growing science.

C. A. CLARKE.

OXYGEN AND THE FOETUS

Oxygen Supply to the Human Foetus. A Symposium Organized Jointly by C.I.O.M.S. and the Josiah Macy Jr. Foundation. Edited by James Walker and Alec C. Turnbull, assisted by Clement A. Smith and Donald H. Baron. (Pp. 313+xii; illustrated. 47s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

The organizers of this conference have called together distinguished workers from several different disciplines, and this book offers reports which illustrate their various approaches to the subject in hand. The book follows the pattern to which we have become accustomed in the reporting of modern symposia.

In order to measure the oxygen supply to the foetus one would like, on the maternal side, the results of measurements of blood flow to the uterus and uterine A-V oxygen differences. Similarly, on the foetal side, one requires umbilical flow and umbilical A-V differences. To complicate the matter further all these readings should be made simultaneously and the mechanisms of the underlying physiological adjustments should be fully understood. Not unnaturally most of the investigators who report their work here have examined one or other of these variables, and in reading the individual articles it is necessary for the reader to keep in mind that the complete picture is not yet available.

There are many very interesting observations in the book, but it suffers from some of the defects consequent upon rapid publication. For example, the verbatim reports of the discussions are on occasions very difficult to follow, and, although it is lavishly illustrated, some of the figures are inadequately labelled and it takes considerable investigation of the text to interpret their meaning.

Despite these strictures it should be appreciated that there is here a great deal of information which is not obtainable in this form elsewhere, and for those who are interested in the physiology of the foetus it provides invaluable additions to our knowledge. Quite apart

from those with a special interest, the book may be recommended to members of the profession who feel that the problems of obstetrics are both understood and solved.

K. W. CROSS.

RADIOACTIVE DIAGNOSIS

Diagnostic Radioisotopes. By Charles A. Owen, jun., M.D., Ph.D.(Med.). (Pp. 425+xix; illustrated. £6 6s.) Oxford: Blackwell Scientific Publications. 1959.

Diagnostic work using radioactive isotopes is carried out by the department of clinical pathology at the Mayo Clinic, and Dr. C. A. Owen, who is associate professor of clinical pathology there, has now written an excellent textbook on the subject. He has managed to cover a difficult and complicated field clearly and concisely and the book is consistently interesting. The necessary introductory chapter on radioactive techniques is followed by detailed considerations of the use of radioactive isotopes for diagnosis in metabolic diseases, haematology, tumour localization, and diseases of the gastro-intestinal and cardiovascular systems. Each section starts with a full and adequate discussion of the physiological and radiological aspects of each test, after which the actual methods are given step by step and in great detail. Numerical examples are included, and the calculations are set out with such clarity that even the least mathematically minded reader will not have any difficulty in following them. Although the book will be very useful on the laboratory bench, it is much more than a laboratory manual. Not only are the relative values of different methods discussed but intriguing suggestions are made where experimental work might be adapted to clinical use.

The author has tried to give at least a mention of all the radioisotopic methods which may be of value to the diagnostician. One might wish that some of these tests —for example, thyroid autoradiography—had been given in more detail, but, as one of the outstanding features of the book is its wealth of references, any deficiencies which an individual reader may discover can easily be righted by consulting the appropriate papers. The tables and figures are well set out and easy to follow. It seems unfortunate, however, that some eight pages of an expensive book have been wasted on four-figure logarithm tables which all readers will surely have in a much more convenient form.

E. V. HULSE.

Dr. Lloyd G. Stevenson in *The Meaning of Poison*—the seventh series of the Logan Clendening Lectures on the History and Philosophy of Medicine—deals with two aspects of his subject: in "Poison, Infection, and Contagion" he traces the history of the ideas these words represent, observing as he does so that the dividing line between pure magic and pure toxicology is sometimes hard to discern. His second chapter, "Hellish Oorali," tells the story of curare from its early history as a South American arrow poison to the present day. Taking his dramatic title from a poem of Tennyson, Dr. Stevenson says that, though this poet may or may not deserve's Auden's harsh comment that he had perhaps the finest ear of any English poet but was also undoubtedly the stupidest, he was extraordinarily sensitive to movements of opinion, and faithfully reflected popular prejudice against the physiological experiments carried out with curare by François Magendie and his pupil Claude Bernard. Dr. Stevenson concludes that, "though Lord Tennyson was horrified, mankind in general surely has reason to be glad." (University of Kansas Press, Lawrence, 1959; 53+vii pp.; price $2.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Electron Microscopy of the Cardiovascular System. An Electron Microscopic Study with Applications to Physiology. By Bruno Kisch, M.D. (Pp. 180+xi; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

A History of Psychiatry. By Jerome M. Schneck, A.B., M.D. (Pp. 196+ix; illustrated. 44s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications 1960.

Electroencephalography in Anesthesiology. By Albert Faulconer, Jr., M.D., M.S., and Reginald G. Bickford, M.B., Ch.B., M.R.C.P. (Pp. 90+viii; illustrated. 38s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Perils of Leadership in Science. By Sir Lindor Brown, C.B.E., F.R.C.P., F.R.S. Sir David Russell Memorial Lecture No. 2. (Pp. 20. 3s. 6d.) London, New York, Toronto: Oxford University Press. 1960.

Neurology Simplified. A Practical Approach to the Early Diagnosis and Treatment of Neurologic Diseases written especially for General Practitioners and Students. By David Joseph Lafia, M.D. (Pp. 175+xx; illustrated. 54s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Diseases of the Nails. By V. Pardo-Castello, M.D., and Osvaldo A. Pardo. M.D. Third edition. (Pp. 284+xxvi; illustrated. 68s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Glossary of Words and Phrases used in Radiology and Nuclear Medicine. By Lewis E. Etter, B.S., M.D., F.A.C.R. (Pp. 203+xv; illustrated. 68s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

The Mentally Subnormal: The Social Casework Approach. Edited by Margaret Adams. (Pp. 271+xvi. 25s.) London: William Heinemann Medical Books, Ltd. 1960.

Principles of Cleft Palate Prosthesis. Aspects in the Rehabilitation of the Cleft Palate Individual. By Cloyd S. Harkins, with the collaboration of William R. Harkins, and John F. Harkins. (Pp. 219+xiii; illustrated. 96s.) New York: Temple University Publications. 1960.

Relaxation for Childbirth. By Mary Barfield, M.Phys.A. (Pp. 149; illustrated. 12s. 6d.) London: William Heinemann Medical Books, Ltd. 1960.

The Search for New Antibiotics. Problems and Perspectives. By G. F. Gause. Trends in Science, vol. II. (Pp. 97+x; illustrated. 38s.) New Haven: Yale University Press. 1960.

Evolution: Its Science and Doctrine. Edited by Thomas W. M. Cameron. Royal Society of Canada "Studia Varia" Series 4. (Pp. 242+xi; illustrated. 40s.) University of Toronto Press. 1960.

Experiences with Congenital Biliary Atresia. By Julian A. Sterling, M.D., Sc.D., F.A.C.S. (Pp. 68+ix; illustrated. 44s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

An Introduction to Physical Anthropology. By M. F. Ashley Montagu. Third edition. (Pp. 771+vi; illustrated. £5 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Maternity Nurse. By Anne Treger. (Pp. 206. 16s.) London: Peter Davies. 1960.

Pediatric Anesthesiology. By M. Digby Leigh, M.D., and M. Kathleen Belton, M.D., in collaboration with George B. Lewis, Jr., M.D., and Edward B. Scott, M.D. Second edition. (Pp. 461+xi; illustrated. 84s.) New York and London: The Macmillan Company. 1960.

Hypertension. Vol. VIII. ***Renal, Electrolyte and Autonomic Factors.*** Edited by Floyd R. Skelton, M.D., Ph.D. (Pp. 150; illustrated.) New Orleans, La.: Louisiana State University School of Medicine. 1960.

Epilepsy and Related Disorders. Vols. I and II. By William Gordon Lennox, A.B., A.M., M.D., Sc.D.(Hon.), with the collaboration of Margaret A. Lennox, A.B., M.D. (Pp. 574+xxv; illustrated. 96s.) London: J. and A. Churchill Ltd. 1960.

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LUMBERING LEVIATHAN

The Minister of Health, Mr. Enoch Powell, struck a note in his first major speech which will find an echo in the minds of most, if not all, of those medical men and women who work in the National Health Service. At the outset he stressed the fact that the N.H.S. "by its very nature as a comprehensive State service, holds out dangers and possibilities of harm as well as opportunities and possibilities for good." By coincidence the B.M.A. Council last week spent some time discussing the work of two committees set up as a reaction to these "dangers and possibilities of harm." The first was the Porritt Committee. In the opening pages of this week's *Supplement* we print the questionary this committee is now sending to a large number of medical and non-medical bodies in an attempt to ascertain the views of informed opinion in the country. The Council also discussed the proposals of the Amending Acts Committee for setting up an alternative medical service. Both the medical profession and the Minister of Health are therefore at one in expressing some uneasiness about the dangers of a monolithic State service.

We have repeatedly stressed in these columns the need for flexibility in any organization of medical services, and therefore especially welcome the fact that the Minister of Health sees that with centralized responsibility and decision, and an administrative machine to secure conformity, the great danger is rigidity. "Policies," he said, "which are formed centrally and executed administratively are bound to be slower to change and less adaptable to alterations of circumstance and demand, than if responsibility were diffused and decisions were independent. The great machine is bound to have a one-track mind, to be cumbrous and unresponsive, to abhor variations, to be insensitive to the world around it."

How refreshing it is to hear a Minister of Health say this sort of thing instead of uttering the usual platitudes about the N.H.S. being the best health service in the world! Though anyone who has heard doctors from other countries tell the General Assembly of the World Medical Association about the way organized medical services are provided in their countries soon comes to realize that in Britain we have much to be thankful for. But the disadvantages of the clumsy State machine are especially dangerous, Mr. Powell pointed out at Llandudno last week, in the field of health and medical care—"a field in which it is the individual mind, the local experiment, even the chance observation, which bring about the great advances." We live in a time of change and ferment, and with consequent alterations in the life of the country there must be corresponding alterations in the content of the health services. But to cope with these, to use Mr. Powell's words, "poor Leviathan is left lumbering behind; for the great machine is bound to be working on a conception of the nation as it no longer is, perhaps as it has long since ceased to be. There is always a time-lag before parliaments, and ministers and bureaucrats, and politicians set off again in pursuit of the world which has moved on."

The Minister went on to say that those who framed the N.H.S. were aware of these dangers and embodied in its structure certain elements of independence as a counterpoise. He instances the contractual status, for example, of general practitioners, and the representation of doctors and other professions in the structure of the hospital and executive council services. The N.H.S. Acts did in fact provide a framework which left room for adaptation and flexibility. But in the 13 years that have passed, the grip of the great machine has tightened rather than loosened, and Leviathan has swollen to unhealthy proportions.

Mr. Powell's diagnosis of the sad state of Leviathan's health at least confirms the accuracy of the prognosis of the critics of State medicine between 1942 and 1948. It is, however, one thing to make a diagnosis and another to decide upon the correct treatment. Mr. Powell wants to see an increase of voluntary work in the N.H.S. and, so it seems, an increase in those who are prepared to help themselves. Though the N.H.S. was intended to be comprehensive, it was not, in his view, intended to be exclusive. He welcomed the fact that medical service and care were available under the N.H.S. "and that completely independent organizations exist in the field, to support and conduct research, to study and criticize, to supplement, assist and (why not?) overlap the services provided by authority of Parliament." He paid a welcome tribute to the valuable assistance given by the Nuffield Foundation, the Nuffield Provincial Hospitals Trust, and the King Edward VII Hospital Fund for London. In the N.H.S. he sees the hospital programme as "the driving shaft of the development of the whole health service." In hospital development

he attached importance to the Building Notes now being issued, notes which "are the work of a new, important and growing element in the Ministry of Health—the Development Unit."

One of Mr. Powell's most interesting observations was on the part to be played in the future by local authorities. In the modern approach to health and medical care he saw three trends running side by side: the growth of community care and after-care of the sick (relieving the work of the hospital); the development of preventive and remedial measures; and third, the more intensive and efficient use of hospital accommodation. He coined the slogan "fewer beds in newer hospitals." The Minister saw these three trends mutually interdependent. The development of two of them lay with the local authorities, and, "if the new trends are to find full expression, the biggest expansion within the health service in the next decade will have to come on the side of local government." One great weakness in all this picture is finance. Mr. Powell—and on finance he speaks with authority—said that the N.H.S. "could not have been devised more effectually if the very object had been to put the three main elements into watertight non-communicating compartments. There are in fact three separate financial systems, and consequently the inter-relation between developments and decisions in each of the three fields is virtually impossible to express in the clear financial terms which would so much help administration and public understanding." The new Minister of Health has kept his first major speech free from cant, and his accurate diagnosis of the weaknesses of the N.H.S. makes us hope that he will remain long enough in office to provide effective remedies.

CORONARY ARTERY DISEASE

In the Jephcott lecture published in the opening pages of this issue Sir Howard Florey looks at coronary artery disease as it presents to the experimental pathologist. Although, as he says, much of his commentary must be (or should be) common knowledge, he puts into clear perspective the results of recent research, and all who have an interest in this subject should read his paper in its entirety. His approach to the problem is to examine two separate, but associated, components of coronary artery disease —alterations in the wall of the artery itself and alterations in the content of the artery.

So far as the arterial wall is concerned, the mechanism of transport of substances in the blood across the continuous cellular barrier of the endothelium is far from clear. Pathologists are undecided whether there is any relationship between fatty streaks in the intima and the later formation of atheromatous plaques. The importance of cholesterol in the development of atherosclerotic lesions in man is unsettled. The remarkable pleomorphic lesions of atheroma and their patchy distribution have never been satisfactorily explained. Mechanical stresses associated with the circulation have received critical attention, and the possibility that mechanical damage to the arteries might initiate lesions that ultimately lead to deposition of fibrin and lipid is one to be seriously considered. The inner layers of arteries may well respond to transient and minor haemodynamic changes, such as increased intravascular pressure or vasoconstriction, as if to injury, and the histological changes observed in early atheromatous lesions are essentially the same as those seen during the repair of injured connective tissue. Studies of the molecular and biochemical phases of the reparative processes of arterial collagen are required to determine what influences initiate these processes within the interstices of the arterial wall, and whether they follow mural deposition of fibrin and the passage of irritative lipid material through the arterial wall.

In considering alterations in the content of the artery, Sir Howard stresses the differences between clotting and thrombosis. A thrombus is an intravascular object with a characteristic structure, whereas a clot is formed by fibrin, which entangles the constituents of the blood in its immediate vicinity. Clots similar to those forming *in vitro* may develop in blood made stagnant by the blocking of a vessel with a thrombus, and so they may be of importance, though secondary, in coronary thrombosis. Many attempts have been made to show that the blood of atherosclerotic patients clots more easily than that of so-called normals, but, even if this were so, it would not mean that it was more apt to deposit a thrombus in a vessel, for this depends on alterations to platelets. *In vitro* tests of coagulation and fibrinolysis do not at present adequately reflect the processes leading to the formation of intravascular thrombosis. There is evidence to suggest that it may be thrombosis rather than atherosclerosis which is increasing and leading to the present high incidence of coronary heart disease. It is important, therefore, to develop experimental methods to study which factors have an effect on platelets and thrombus formation and also to study thrombolysis and the intrinsic anticoagulant property of the arterial wall.

Sir Howard inquires whether the enormous number of observations and experiments already recorded have given us anything firm on which to base preven-

tion and treatment of coronary artery disease. Although certain developments are promising, the honest answer at present is in the negative. At the start of his lecture he quotes from a review, remarkable for its clarity and perspective, written by Professor T. P. Hilditch and Dr. H. Jasperson. "Faced with a problem of such extreme complexity . . . it seems both unfortunate and surprising that some medical investigators have been prone to seize one or other facet of the problem and thereon to formulate hypotheses incongruous with the slender weight of the experimental findings on which they are based." Those who declare that in ten years or so the causes of coronary atherosclerosis and of coronary thrombosis will be known and that treatment and prevention will be effective should take this rebuke to heart. Coronary disease has news value and is often given dramatic headlines and exaggerated commentaries in the popular press. In the United States the public is constantly being bombarded with half-truths about coronary heart disease, and by now there cannot be many who have not heard something about cholesterol. Since many will agree with Sir Howard that we are still in a state of much confusion, it is all the more important for members of the medical profession, who are also faced by the over-eager canvassing of some pharmaceutical firms, to regard all unsubstantiated theories with proper detachment.

This is also a matter of great importance to those who undertake clinical trials of new drugs and diets in patients with coronary heart disease. Three main types of clinical trial are commonly made: one is designed to determine whether a certain diet or drug will reduce the plasma cholesterol levels; another attempts to test the efficiency of anticoagulants in reducing a thrombotic tendency; and the third studies the effect of a certain drug on the incidence of angina. Most of the investigations of cholesterol-lowering agents have been short-term studies, and at present there is nothing to indicate that any drug or dietetic regime has a beneficial effect on the development of human atherosclerosis or on the incidence of thrombosis. As Sir Howard Florey emphasizes, we badly need well-planned observations on a very considerable scale to settle these points. The only convincing evidence of a beneficial effect in the human will be a clear-cut reduction in the incidence of myocardial infarction with support from electrocardiographic or necropsy records. So far as anticoagulants are concerned, there is still no general agreement about their advantages in patients with angina or myocardial infarction, and it is possible on theoretical grounds that a substance which prevents platelet agglutination might be of greater benefit. As to angina, experienced physicians know that it is notoriously variable and will respond to almost any pill. Uncontrolled clinical trials, such as several recently reported, of drugs which are claimed to reduce the incidence of angina are largely a waste of time and should be discouraged. Moreover, gratuitous comments on improvement in the incidence of angina during the course of studies designed to lower the serum cholesterol or the trials of anticoagulant therapy are often valueless, since they are seldom accompanied by evidence from controls. It is important, therefore, to continue to study the problems of coronary heart disease objectively, as Sir Howard Florey has so usefully done.

INTERFERON

Infection with one virus may afford protection against a superimposed infection with another virus. Medical literature records a number of observations by Edward Jenner[1] and others[2] which may have been examples of this phenomena, but the first experimental evidence in favour of virus interference was recorded only twenty-five years ago by F. Magrassi[3] and M. Hoskins.[4] In 1937 G. M. Findlay and F. O. MacCallum[5] made their important observations that mutual interference could be demonstrated between two antigenically distinct viruses—namely, those of Rift Valley fever and yellow fever. This could be ascribed only to cellular immunity. During the ensuing years the interference reaction provided a model for the study of host–virus reactions,[6] and in doing so brought back into perspective the importance of cellular immunity in acquired resistance.

In 1957 A. Isaacs and J. Lindenmann,[7] working at the National Institute for Medical Research in London, made an important discovery which pointed to a possible mechanism of virus interference. They found that, if fragments of chick chorio-allantoic membrane were incubated with heat-inactivated influenza virus, a substance was released from the cells which had antiviral properties. They called this interferon. Confirmatory evidence has since come from many quarters, and it is now known that interferon can be produced from many different cells, including those from man, monkey, and chick, and from a number of different interfering viruses,

[1] Jenner, E., *Med. phys. J.*, 1804, **12**, 97.
[2] Henle, J., *On Miasmata and Contagia*, 1840, translated by George Rosen, Baltimore, 1938.
[3] Magrassi, F., *Z. Hyg. Infekt.-Kr.*, 1935, **117**, 501.
[4] Hoskins, M., *Amer. J. trop. Med.*, 1935, **15**, 675.
[5] Findlay, G. M., and MacCallum, F. O., *J. Path. Bact.*, 1937, **44**, 405.
[6] Henle, W. A., *J. Immunol.*, 1950, **64**, 203.
[7] Isaacs, A., and Lindenmann, J., *Proc. roy. Soc. B*, 1957, **147**, 258.
[8] —— and Burke, D. C., *Brit. med. Bull.*, 1959, No. 15, 185.
[9] Porterfield, J. S., *Lancet*, 1959, **2**, 326.
[10] Isaacs, A., and Westwood, M. A., ibid., 1959, **2**, 324.
[11] Canell, K., and Tommila, V., ibid., 1960, **2**, 682.
[12] Isaacs, A., and Hitchcock, G., ibid., 1960, **2**, 69.
[13] Hitchcock, G., and Isaacs, A., *Brit. med. J.*, 1960, **2**, 1268.

including myxoviruses, enteroviruses, arborviruses (arthropod-borne), and several others. The interfering virus used to make interferon in the cell culture may be live or inactivated.[8] The antiviral activity of interferon can be demonstrated *in vitro* by tissue-culture techniques employing a suitable challenge virus, which will serve to distinguish control from interferon-treated cultures.[9] By these methods it can be shown that interferon is active against a wide range of viruses, herpes simplex being a notable exception.

The action of interferon *in vivo* has also been studied. Isaacs and M. A. Westwood[10] showed that interferon would inhibit the growth of vaccinia virus in the rabbit's skin, the effect being maximal with interferon made from the same species (i.e., rabbit) given prior to and at the site of challenge. This work has been confirmed, and recently K. Cantell and V. Tommila[11] have shown that the rabbit's eye can be protected against vaccinia-virus infection with rabbit interferon given immediately after infection and for four consecutive days. No protection was observed with herpes simplex virus under identical conditions. Mice infected intranasally with influenza viruses in suitably graded doses produce first fresh infective virus, then interferon, and then antibody in their lungs. Isaacs and G. Hitchcock[12] found that interferon appeared in the lungs after the peak titre of virus but several days before the appearance of antibody. They concluded that interferon may play an important role in limiting infection and thus aid recovery. In a more recent report, published in this journal last week,[13] these same workers have followed up these experiments in mice by studying the effect of interferon, administered passively and also induced by active infection, against challenge with a virulent encephalitis virus. In both cases protection was observed, but of particular interest was the fact that interferon induced by intranasal inoculation of avirulent influenza virus protected mice against the lethal action of the challenge virus given intraperitoneally. Furthermore, a number of animals that survived developed antibody, so presumably the natural immune mechanism was not impaired.

Interferon is a viral antibiotic in the experimental stage and has many interesting properties. It is a protein but non-antigenic; it is fairly stable to changes in *p*H and temperature, and has a wide range of activity against viruses when tested *in vitro*.[8] On the debit side there is evidence that its range of action may be determined by species specificity, though this may not prove to be crucial when methods of production and assay have been further developed. Experimentally the effectiveness of interferon has been shown to be bound up with the time relationship between treatment and challenge, with dosage and site of administration. Clearly these factors will be of importance if and when interferon, or something related to it, comes to be used in human beings. These are some of the points which need intensive study, but, as these recent reports show, a start has been made, and an encouraging one as well.

SURGICAL TREATMENT OF HYDROCEPHALUS

Hydrocephalus most commonly presents as a congenital anomaly or develops in early infancy as a result of developmental malformation of the central nervous system. It may also follow meningitis, though the incidence of this complication is lower than in the pre-antibiotic era, and sometimes it is secondary to intracranial neoplasm. For many years surgeons have been striving to cure this distressing condition by operation, but unfortunately no really satisfactory treatment has yet been devised, though some progress has been made. Most of the so-called modern operations for hydrocephalus had been already attempted before the first world war, but success was achieved only with the introduction of plastic materials into the surgical armamentarium. During the last two decades many drainage procedures were reintroduced, but only four have brought any success.

In 1939 A. Torkildsen[1] described ventriculo-cisternostomy for non-communicating hydrocephalus. This procedure is still used by some surgeons for hydrocephalus secondary to tumours; it is rarely practicable in children with congenital hydrocephalus because of the small size of their cisterna magna. Drainage of the cerebrospinal fluid through a tube into a ureter after nephrectomy has been popularized by D. D. J. Matson.[2] One of the disadvantages of this operation is that there is a constant and considerable loss of electrolytes from the body. If the cerebrospinal fluid is drained into the peritoneal cavity[3] there is no loss of salts, and this operation has therefore been popular with many surgeons all over the world. Unfortunately, the various plastic tubes used for drainage cause a peritoneal reaction, and blockage of the drain by adherent omentum or intestine has been common. Theco-ureteric and theco-peritoneal shunts for communicating hydrocephalus have been successful in about a third of the

[1] Torkildsen, A., *Acta chir. scand.*, 1939, **82**, 117.
[2] Matson, D. D. J., *J. Neurosurg.*, 1949, **6**, 238.
[3] Shenkin, H. A., Spitz, E. B., Grant, F. C., and Kety, S. S., *J. Neurosurg.*, 1948, **5**, 466.
[4] Spitz, E. B., *Pediat. Clin. N. Amer.*, 1959, **6**, 1215.
[5] Carrington, K. W., *J. Mich. med. Soc.*, 1959, **58**, 373.
[6] MacNab, G. H., *J. Neurol. Neurosurg. Psychiat.*, 1959, **22**, 82.
[7] Rickham, P. P., *Wien. klin. Wschr.*, 1960, **72**, 573.
[8] Laurence, K. M., *Lancet*, 1958, **2**, 1152.
[9] Rickham, P. P., and Roberts, J. R., *Brit. med. J.*, 1960, **1**, 1887.

operated cases. However, most cases of hydrocephalus in infancy are of the non-communicating type, and ventriculo-ureteric and ventriculo-peritoneal shunts have been successful only in a very small percentage of cases.

The truly physiological solution of the problem is drainage of the cerebrospinal fluid into the blood-stream. During the first half of the century this method was attempted many times, but without success, because blood entered the tube and clotted. It was therefore realized that a one-way valve must be incorporated in the drainage system. During the last decade several such valves have been introduced. That developed by Spitz and Holter,[4] composed of a special silicon rubber which is less irritant to the body tissues than any plastic hitherto devised, has proved to be a great advance on former methods. Over 5,000 operations for hydrocephalus using the Spitz–Holter valve have by now been performed on both sides of the Atlantic. With this technique it is immaterial whether one is dealing with a communicating or a non-communicating type of hydrocephalus, as the cerebrospinal fluid is drained from the right lateral cerebral ventricle via the internal jugular vein into the lower end of the superior vena cava or the right atrium. The valve ensures that drainage is gradual and there is no danger of a rapid fall of the intracranial pressure. The operative mortality is very low, and the operation, which is a relatively minor procedure, is well tolerated even by newborn infants. It appears from the published early results[5–7] that the operation is successful in at least four-fifths of cases.

In recent years the short-term results of operations for hydrocephalus have therefore greatly improved. Mr. A. R. Taylor and his co-workers point out in the article at page 1356 of the *Journal* this week that little is known about the long-term results of modern drainage operations. The Spitz operation has been practised for five years only, and most surgeons with a large experience of other drainage operations have only comparatively recently changed to the valve operation. Therefore some years must pass before we have precise information about the real benefit that these procedures give.

An appraisal of the results of surgery is made more difficult by the fact that some cases of hydrocephalus undergo spontaneous arrest. K. M. Laurence[8] reviewed 182 cases of untreated hydrocephalus seen at one centre. He found that 48.8% of the total were dead and 44.5% had undergone spontaneous arrest. Only 18.1% of the total number of cases reviewed were of normal intelligence. As P. P. Rickham and J. R. Roberts have pointed out,[9] any worth-while operation for hydrocephalus must therefore achieve arrest in more than 44.5% of the cases, and more than 18.1% of the operated children should be of normal intelligence.

In the light of our present knowledge it is not surprising that there are many different opinions about the selection of cases of hydrocephalus for operation. Should we wait for spontaneous arrest? For how long should we wait? In many cases arrest will only take place when the child is completely crippled. Obviously every case has to be considered on its merits. Careful clinical and neurological examination, weekly measuring and charting of the head circumference, and, if necessary, repeated intraventricular pressure readings have all to be employed. After a few weeks of careful observation it should become evident whether the rate of expansion of the head is increasing, decreasing, or remaining the same. Individual variations are so great that it is unlikely that a scheme or formula can be devised to indicate which case will undergo early spontaneous arrest and which continue to progress.

FATAL REACTIONS TO DRUGS

Deaths from therapeutic misadventure are the subject of some instructive statistics in the latest annual commentary to come from the Registrar-General for England and Wales.[1] In the two years 1957–8 there were 265 deaths due to adverse reactions to drugs or therapy. The deaths attributed to "therapy" comprised 39 from *x*-radiation, 20 from blood transfusion, and 11 from electro-convulsive treatment. Prominent among the drugs causing death was chloramphenicol, which continued to show its lethal potentialities in causing 13 deaths; the causes were blood dyscrasias and in one case a hypersensitivity reaction. Chlorpromazine on its own caused 10 deaths, in conjunction with reserpine 1, and with pecazine 1. In addition pecazine by itself caused 3 deaths. Anticoagulants caused death in 9 cases plus another 2 when administered with other drugs; as would be expected, most of these were due to haemorrhage. The antirheumatic drug phenylbutazone was responsible for 5 deaths when given on its own, for 1 in conjunction with meprobamate, 1 with gold, and 1 with gold and salicylates. Gold itself caused 4 deaths. The 16 deaths attributed to insulin included 14 in coma; the other 2 were from acute heart failure and pulmonary oedema. The sulphonamides were another group causing several deaths, there being 10 cases in this category. The 8 deaths caused by penicillin were all due to hypersensitivity reactions. Among the many other types of drugs causing fatal reactions were steroid hormones, antithyroid drugs, iron preparations, aspirin, mersalyl, and cytotoxic drugs. The commonest fatal

[1] *Registrar-General's Statistical Review of England and Wales for the Year 1958. Part III. Commentary*, 1960. H.M.S.O., London. 13s.
[2] Ibid., 1958. H.M.S.O., London.
[3] U.S. Department of Health, Education, and Welfare. Food and Drug Administration. (21 CFR Part 1, 130). Enforcement Regulations Drugs and Devices, New Drugs. Notice of Proposal to Amend Labelling Requirements, 1960.

response to a drug was blood dyscrasia, and after that a hypersensitivity reaction.

The previous inquiry[2] of this nature covered three years instead of the two now reported on, so that the 302 deaths then recorded as due to therapeutic misadventure cannot be exactly compared with the 265 recorded now. But the present total does suggest that deaths of this kind are increasing in incidence. In general, much the same groups of drugs were found to be causing fatal reactions in the earlier inquiry — sulphonamides, penicillin, chloramphenicol, insulin, anticoagulants, phenylbutazone, steroids, antithyroid drugs, chlorpromazine. Obviously such drugs as these—among the most effectual in modern therapy—are often indispensable in the treatment of a patient. But their toxicity, and that of many other recently introduced drugs which also cause fatal reactions, needs emphasizing from time to time. It is interesting to note that the Food and Drug Administration of the U.S.A. has recently proposed regulations[3] which would, among other things, draw the hazardous properties of a drug to the physician's attention by means of suitable wording on the label of its container.

END OF THE BOARD OF CONTROL

The Mental Health Act, which came into operation on November 1, and on which we commented last week,[1] was largely based on the recommendations of the report[2] of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency. Under the Act the Board of Control disappears, and in advising that the time had come to abolish it the Royal Commission paid this tribute to its work:

> "Those who have taken part in the work of the Board of Control may well look back with pride to the part which the Board has played since 1913 in the development and improvement of our mental health services during a difficult period. We hope that they, and all who know what valuable work they have done, will welcome our recommendations for a different future organization, which should make it possible to pursue the same general aims by methods more suited to the conditions of our time."

The Board met for the last time on October 25. Under a lay chairman, Sir Frederick Armer, the Board has comprised four senior commissioners with medical or legal qualifications: the senior commissioner was Dr. the Hon. W. S. Maclay, and the other senior medical commissioners were Dr. W. Rees Thomas and Dr. Isobel Wilson. The work of the Board has been going on for well over a hundred years, for though it was not set up under its present title until after the passing of the Mental Deficiency Act of 1913, it continued to carry out functions under the Lunacy Acts previously undertaken by the Lunacy Commissioners. The English law concerned itself with people of unsound mind from very early times, but the Lunacy Commissioners did not come into existence until 1845, when Lord Ashley, later the seventh Earl of Shaftesbury, was appointed their first chairman. It was Lord Ashley who introduced into Parliament the two Bills which later became the Lunacy Acts of 1845. The main functions of the Board of Control up to the coming into force of the National Health Service Act were to supervise mental health services of local authorities, to register and inspect voluntary mental hospitals and homes, and to concern itself with the liberty of the subject and with legal procedures applied to individual patients. Since 1948 the Board's work has been mostly connected with the last of these functions and with the administration of three special State hospitals—Broadmoor, Rampton, and Moss Side.

Miss Edith Pitt, Parliamentary Secretary to the Ministry of Health, attended the last meeting of the Board and added her tribute to those it has already received. "The fact that the Board is now disappearing," she said, "is due in large measure to the success with which it has performed its duties." And Lord Kilmuir, the Lord Chancellor, in a written message, remarked that the work of the Board required not only diligence and patience, but great human qualities and intelligence. He continued: "I welcome this opportunity of recording the gratitude of my predecessors and myself to the members and officers of the Board for the admirable way in which they have discharged their duties." The Board of Control, which has always been wide open to public criticism, deserves these just tributes, and its members can lay down their considerable burden with the knowledge that those who were in the best position to appreciate their services are the most regretful at their departure.

QUESTIONS FROM THE PORRITT COMMITTEE

The Medical Services Review Committee's questionary, reproduced in this week's *Supplement*, is a reminder that this body, though silent, has not been inactive. As the introductory letter states, the Committee has now reached a stage when it is anxious to compare its own tentative views with those of others "on a number of matters of fundamental importance." This is in line with the Committee's intention when it began work two years ago to seek opinions wherever it might usefully find them. As its chairman, Sir Arthur Porritt, told the Council of the B.M.A. last week, his committee wants to know what the workaday doctor, among others, thinks about the system in which he practises.

The Porritt Committee was asked by its nine medical sponsoring bodies "to review the provision of medical services to the public, and their organization, in the light of ten years' experience of the National Health Service, and to make recommendations." At the outset Sir Arthur Porritt made it clear[1] that he and his Committee looked upon their terms of reference as demanding more than merely carrying out yet another investigation into the operation of the N.H.S. They interpreted them as requiring a review of the practice of medicine "in all its aspects and in all fields, clinical, social, and preventive, both within and outside the N.H.S." Sir Arthur said they would try to find out what advantages, and what disadvantages, the changing

[1] *Brit. med. J.*, 1960, **2**, 1297.
[2] *Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency, 1954-1957*, 1957. H.M.S.O., London.

[1] *Brit. med. J.*, 1959, **1**, 112.

pattern of medical practice had brought to the patient, the community, and the doctor.

The Committee is now reaching a stage where its report is beginning to take shape, and the present questionary will enable it to compare its tentative opinions with those of others most able to contribute something of value. It is being sent to over one hundred organizations of various kinds, medical and lay, which between them represent a range of experience which leaves few, if any, worth-while sources of information untapped. Replies have been asked for by the end of the year, and a good response will give the Porritt Committee information which should add much to the objectivity of its final report.

FIRST-AID TREATMENT OF BURNS

First-aid treatment implies temporary care which will be followed shortly by definitive treatment: it is given to potentially serious injuries and is often different from the treatment for minor injuries of the same nature. Many minor domestic burns are insignificant and require no first-aid. Their treatment need only be a protective dry dressing of gauze and adhesive strapping, with or without an antibacterial ointment to prevent sticking. So far as we know at present there is nothing that appreciably hastens healing: the point of the dressing is to protect against further mechanical, chemical, or bacterial damage.

First-aid treatment for a burn needing and awaiting medical care (unfortunately doctors may see many burns in this category on Guy Fawkes night) should include reassurance, the relief of pain, and protection from bacterial contamination. Usually the first-aider can best relieve anxiety by taking control of the situation with sympathy and understanding, and ensuring that the patient will have expert care as soon as possible. Speed is especially important when the burn extends over more than one arm or half the front of the trunk. Linked with reassurance is the relief of pain, which is severe only when the burn has caused erythema or has raised blisters. Extensive deep burns often have no pain owing to destruction of the nerve endings. Cold is the best antidote for pain, and putting the burned part under the cold tap is usually the cleanest way of cooling. There is no evidence that compresses of sodium bicarbonate, milk, white of egg, and so on are superior, and the cleaning which may be needed after the use of these substances encourages bacterial contamination. Without cooling, pain usually passes off in one to six hours, to return only if infection sets in. Covering the burn at once with a sterile dressing or a freshly laundered handkerchief, towel, or sheet is a third first-aid measure directed towards preventing bacterial colonization of the recent wound. It is by far the most important measure and the only one, apart from speedy transfer to hospital of a patient with a large burn, which is likely to influence mortality.

Claims have been made that cold may also arrest the progressive damage that follows burning—if such, in fact, is part of the pathology of burns. A. G. Shulman[1] has the impression that "the usual inflammatory process secondary to the burn can be reduced in degree and, indeed, at times reversed by ice-water therapy," and F. L. Willington[2] claims that immersing the burned part in cold milk seems to "exert a limiting action on the injury process" and "produce a phase of regression in the normal sequence of events." There is at present inadequate evidence to support these suggestions, though they cannot be ruled out. The comparison of the effects of a treatment with what previous clinical experience leads the observer to expect is notoriously misleading. The truth in this matter is probably only discoverable by a controlled trial—possibly in human volunteers—with burns of standard degrees of severity.

[1] Shulman, A. G., *J. Amer. med. Ass.*, 1960, 173, 1916.
[2] Willington, F. L., *Brit. med. J.*, 1960, 2, 277.

SUPPLEMENTARY PROFESSIONS

After a long and occasionally contentious course, the proposals to give statutory recognition to that group of devoted workers known as medical auxiliaries have come to a conclusion. The Professions Supplementary to Medicine Act has reached the Statute Book, its title suitably reflecting the new status of these workers. Much credit is due to the Board of Registration of Medical Auxiliaries, as well as to those members of the Cope Committee and committees in the B.M.A. who puzzled for many long hours over the problems, for this culmination to the work of those in the B.M.A. who helped start a "register of technicians" more than a quarter of a century ago.[1]

The groups covered are the chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, and remedial gymnasts. During the preparation of the Bill the speech therapists preferred to opt out of its jurisdiction because they find their present arrangements adequate for the training and discipline of their members; the almoners also have long-standing arrangements for the regulation of their group and have remained outside. The new Act provides a separate board for each of the seven professions concerned, and a council to supervise the boards. Each board will keep a register of members and have power to approve training courses and qualifying examinations. It is also responsible for discipline through two committees, one an investigating body and the other the disciplinary committee. The first of these determines whether a case should come before the second, which has the power to remove an offender's name from the register. Provision is made for appeal to the Judicial Committee of the Privy Council. Thus the procedure is similar to that governing members of the medical profession, as are the categories of offence for which a person may be struck off the register (conviction in a British court of a criminal offence, and guilty of infamous conduct in a professional respect). The council will not only supervise the boards but make recommendations to them. Both it and the boards are subject in some respects to directives from the Privy Council, notably in relation to training and qualifications.

[1] *Brit. med. J.*, 1933, 2, Suppl. 58. [2] Ibid., 1959, 2, 1164.

One of the main causes of argument in the past was the composition of the council. The medical profession wanted a greater preponderance of medical men on it than the other interests wished to concede. When the Bill was drawn up, the medical view did not prevail,[2] but in its passage through Parliament some small concessions to it were made in the House of Lords. The amendments made there and accepted by the Commons specified that registered medical practitioners, and not merely "persons," must be appointed by the English Royal Colleges (three), the Scottish Royal Corporations (two), and the G.M.C. (one), and also required one of the three members appointed by the Government health departments to be a medical man. Therefore out of 21 members 7 must be laymen, 7 must be medical practitioners, and 7 will be appointed severally by each of the boards to contribute in particular the views of the supplementary professions. The boards vary in composition. The B.M.A., for instance, appoints one member each to the chiropodists' and physiotherapists' boards; the Royal Colleges and Corporations appoint members to every board, the Society of Medical Officers of Health one each to the chiropodists' and occupational therapists'. It is noteworthy that one member on every board must be an "expert in professional education."

The great majority of medical auxiliaries work in the Health Service, and they will have to obtain State registration under the new Act; some of those few in private practice will no doubt wish to do so as well. A person not on a register may still practise privately one of these supplementary professions provided he does not claim to be State-registered. But all in the supplementary professions probably welcome the existence of the Act, whether they intend to enjoy the advantages of registration under it or not, for it can only encourage the development of the professional status that many medical men have long sought for these highly skilled members of the medical team. The main risk is whether it may also encourage specialization outside the control of the doctor, on whom ultimate responsibility for the patient rests.

OVERSEAS APPOINTMENTS

Last week the Colonial Secretary announced in a White paper[1] his proposals for halting the loss of experienced government officers from overseas colonial and dependent territories now approaching independence. These territories (subject to minor exceptions) are being offered agreements, to come into effect next April, whereby the British Government undertakes to contribute between £12m. and £16m. a year towards the cost of retaining overseas administrators and technical and professional experts until experienced local staff can be trained to replace them. The agreements, which may affect up to 21,000 pensionable and "contract" officers overseas, including doctors, will be for "perhaps ten years," and the exact details will be individually negotiated with each local government. Put broadly, the offer is to reimburse the full difference between expatriate and local rates of pay, the full cost of education and children's allowances, half the cost of specified passage moneys, and, perhaps of most importance, half the cost of compensation for loss of career on premature retirement resulting from the territory's progress towards independence. The offer is, in fact, one of technical aid in its most valuable form—key people. At the same time the financial provisions are expected to temper local political prejudice against the inevitably higher pay of expatriate officers. Mr. Macleod regards these proposals as the most important outcome of his first year at the Colonial Office, and expects most local governments to welcome them.

Doctors are unlikely to share the Colonial Secretary's satisfaction, however much they may applaud generous and timely aid to developing countries. The one fundamental safeguard they need—a fair chance of a decent job in Britain on their return from service overseas—is not forthcoming. The White Paper dismisses the idea of a Home-based Overseas Service as impracticable, and offers instead expressions of vague good will, exhortations to industrial employers, and the services of agencies such as the Overseas Services Resettlement Bureau. All this has little relevance to the special plight of the doctor. Returning doctors, as Professor Mekie has recently stressed,[3] are faced with an established National Health Service, into which after many years abroad it is not easy to fit. Alternative employment scarcely exists. Medical patronage is now almost completely in the hands of the State. A similar hazard faces the young man who goes out, highly qualified, to serve for a shorter period in some overseas territory. He stands to forfeit his rightful place on the promotion ladder. Despite the largely attended conference called by the B.M.A. two years ago to discuss the filling of medical posts overseas,[3] when these very difficulties were plainly stated, the Government continues to show a cynical disregard for the welfare of these doctors who are so badly needed. It is little use the B.M.A. offering travelling scholarships[4] to encourage service overseas, while the Government fails to do its part. Surely between them the Colonial and Commonwealth Offices and the Ministry of Health could devise some way of underwriting these overseas medical appointments. Is a Home-based Medical Overseas Service, perhaps on the lines Dr. Morton Mitchell suggests,[5] so very fanciful?

DR. H. GUY DAIN, 90

To-day, at the age of 90, Dr. Dain looks very little different from the photograph we reproduced in the *Journal* on his eightieth birthday. He is as compact as ever in body and mind. His influence in the development of the B.M.A. has been a decisive one. Two or three of those who have worked closely with him send him messages of congratulation in this issue (see p. 1377). And the *Journal* adds its own, wishing him at the same time many happy and active years to come.

[1] *Service With Overseas Governments*, Cmnd. 1193, 1960. H.M.S.O., London. Price 1s. 3d. net.
[2] *Brit. med. J.*, 1960, 1, 1274.
[3] *Brit. med. J. Supplement*, 1958, 2, 220.
[4] Ibid., 1960, 1, 187.
[5] *Brit. med. J.*, 1960, 2, 67.

[H. J. Whitlock and Sons, Birmingham

H. GUY DAIN, M.D., LL.D., F.R.C.S.

Dr. H. Guy Dain will be 90 years of age on November 5. Dr. Dain was elected a member of the British Medical Association on April 15, 1896. He became Chairman of the old Insurance Acts Committee of the B.M.A. in 1924, a post he filled for 12 years, and he was also Chairman of the Conference of Local Medical and Panel Committees from 1919 to 1924. His membership of the I.A.C. and its successor, the General Medical Services Committee, concluded only when he decided not to seek re-election this year. He was Chairman of the Representative Body from 1937 to 1942. A member of the Council of the B.M.A. since 1921, he was its Chairman from 1943 to 1949. This year he told the Representative Body that he would not stand for re-election.

Dr. Dain has been a Direct Representative on the General Medical Council since 1934. He was awarded the Gold Medal of the B.M.A. in 1936 in recognition of his outstanding services to the Association. In 1957 he became the first recipient of the Claire Wand Award for his outstanding services to general practice. The honorary degree of LL.D. was conferred on him by the University of Aberdeen in 1939, and the honorary degree of M.D. by the University of Birmingham in 1944. He was admitted a Fellow of the Royal College of Surgeons of England in 1945, as a Member of more than twenty years' standing.

Tributes from Old Colleagues

Dr. the Rt. Hon. CHARLES HILL, M.P., writes: It is nearly 30 years since I first saw the Insurance Acts Committee in action. Just arrived on the B.M.A. staff, I sat baffled and bewildered by the appalling complexity of it all. But not so the Chairman, as serene as he was small and a master of it all—including the Committee. It was Guy Dain. Throughout my 18 years with the B.M.A., Guy Dain played a dominant part in one high office after another. Unruffled and unrattled, never lost for a fact, it was his wisdom, his common (yet so uncommon) sense which stuck out a mile. An image of him that I carried away from the B.M.A. was one of steadfastness, dependability, rock-like reliability. He was trusted by everyone.

The past tense of these words suggests an obituary. Far from it. He is 90 years young, with years of life and vigour ahead. He must have been nearly 80 when he told me one day that that evening he would be having a chat with his mother. Happy birthday to Guy Dain!

Dr. J. A. BROWN writes: Meeting Dr. Guy Dain to-day and noting his apparently undiminished energy, his keen interest, and his grasp of the essentials of a problem, it is difficult to believe he is about to celebrate his ninetieth birthday.

I have known Dr. Dain since shortly before he became chairman of the Birmingham Panel Committee in 1915—one of his first steps in medical politics. This committee had had a chequered and unhappy career, and its relations with the Birmingham Insurance Committee were far from friendly. In Dr. Dain's hands the Panel Committee soon became a force to be reckoned with, and relations with the Insurance Committee gradually improved; the good understanding which exists to-day between the doctors and the local executive committee are the result of the foundations laid by Dr. Dain many years ago.

Dr. Dain's further rise to fame is well known to all, and it is a striking fact that his work has been accomplished without the spectacular incidents that might have been expected in a fighting life.

He has had many fights with ministerial and other opponents, but he has always kept his gloves on and has never seemed to lose his temper, even during stormy sessions which occurred during the negotiations over the National Health Service, when the temptations to do so were almost overpowering.

It would be difficult to estimate fully the extent of the influence which Dr. Dain's work has had on the medical life of Birmingham; his example has inspired many to give as fully and as freely of their time and energy as he did—it is an influence which is not likely to diminish with the passage of time.

All in Birmingham will join with me in wishing him many more years of health and happiness.

No Tricks of Showmanship

Dr. E. A. GREGG writes: Among the many recollections associated with Guy Dain which come to my mind there are some that stand out with particular distinctness.

Soon after the 1914–18 war we were faced with one of those periodic reviews of the capitation fee under the N.H.I. I well remember the debate in the old council room in the Strand, with Brackenbury in the chair of the Insurance Acts Committee. We were offered one of two alternatives as capitation fee by the Minister of Health, Joynson Hicks (as he then was). Neither alternative was to our liking and we asked for arbitration, which was refused. Dain strongly advocated resignation from the service, and stood to his guns in spite of much opposition from prominent influential members of the I.A.C. He won his point, and we collected almost 100% resignations, which were placed in the hands of the secretaries of panel committees to be forwarded to the Ministry if our demand for arbitration

was still rejected. We asked again and got what we wanted. Meek submission to Ministry domination received its first serious blow, and Guy Dain won his place as a trusted leader and has held it ever since.

Another recollection is associated with the court of inquiry under the late Lord Amulree, when Dain presented the profession's case for increased remuneration. I well remember a hot Saturday afternoon at the Ministry after some days of cross-examination. Dain was due to make his final speech to close the proceedings, and, although it was suggested to him that he might wish to leave it over until Monday, he elected to go on when the affairs were fresh in mind. We had not the advantage in those days of having this kind of thing done for us by distinguished legal luminaries. We got no satisfaction in the end when Lord Amulree's decision was announced. We might as well have been told what it would be without waiting for weeks, and it was generally believed by many that the whole "inquiry" was largely eyewash, and the result determined beforehand. Dain did his part splendidly and earned our gratitude again.

The efficient and painstaking discharge of his duties as chairman of the negotiating committee on behalf of the profession at the introduction of the N.H.S. is still almost recent history. As chairman of the I.A.C. and of the Representative Body he won golden opinions on all sides. Wisdom and sound common sense characterized all his words and actions. No tricks of showmanship or oratory have been there. Our warmest and most grateful feelings will always be aroused when we have occasion to remember his services, and he has our good wishes for his health and happiness now and always.

As Chairman of Council

Dr. S. WAND writes: In years of service alone, Guy Dain must be nearly unequalled in the work he has done for the Association and the profession as a whole. I have always counted myself fortunate to have worked under him, and his outstanding term of office as Chairman of Council set a splendid example for those of us who follow him. The calm alertness of his manner, the conciseness of his speech, and his sensitivity to the feeling of a meeting—these are qualities which I most admire in him.

What made him, in the opinion of many of us, the best chairman of committee under whom we have served? I think first and foremost it is because he is a born leader, a quality shown in his chairmanship of the Negotiating Committee during the introduction of the National Health Service. Second, that he always rapidly acquired a full grasp of the subject under discussion: if it was wanted, he was ready with an answer to the problem, and so he had the facility of being able to unravel the most tangled debate.

He is not one to play to the gallery, nor does he attempt the histrionic. Rarely have I heard him make an ineffective speech, never a bad one—he has always spoken to the point, and almost invariably with a new and refreshing angle.

For many years we travelled together to and from meetings. I learned a lot about him—about his affection for young people and his interest in helping to further their aims and ambitions, and his appetite for new ideas and for aiding in their fulfilment.

The doyen of the B.M.A., I am proud to have worked alongside him and to have this opportunity of thanking him for his tutelage.

ROYAL ARMY MEDICAL COLLEGE

QUEEN MOTHER AT CENTENARY

On October 2, 1860, the Practical Army Medical School at Fort Pitt, Chatham, was founded. From this foundation sprang the present Royal Army Medical College at Millbank. The Centenary was celebrated on October 26, when QUEEN ELIZABETH THE QUEEN MOTHER, in her capacity as Colonel-in-Chief of the Royal Army Medical Corps, attended a ceremonial parade and prizegiving at the College at Millbank.

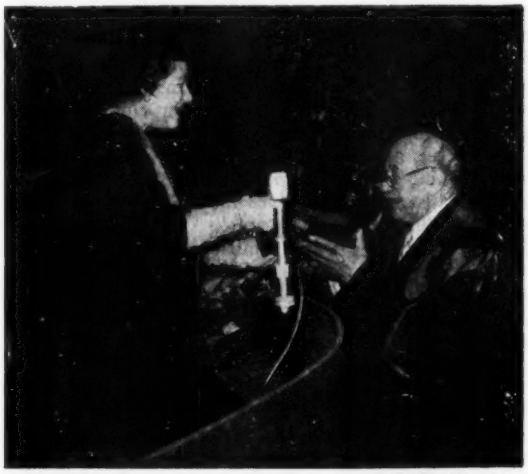
Evolution of the College

It was through the efforts of Florence Nightingale that the Practical Army Medical School was created. Deeply

[*Photographic News Agency, Ltd.*

FIG. 1.—The Queen Mother inspecting her Guard of Honour at Millbank Barracks in heavy rain.

perturbed by the poor standards of training of Army medical officers, especially in preventive medicine, she succeeded, in spite of the strongest opposition, in imposing her will. Eventually she was entrusted with the task of drawing up the regulations for the School and she was even allowed to nominate the professional staff. The siting of the School



[*Soldier Magazine*

FIG. 2.—Sir Stanford Cade receiving the Guthrie Award.

at Fort Pitt was determined by the fact that at Chatham were to be found the sick and wounded evacuated from overseas. The main function of the school was to give newly joined medical officers courses of instruction in military surgery and medicine, pathology, and hygiene.

In 1863 the School moved to Netley, where it was incorporated in the Royal Victoria Hospital, but after the Boer War the Army Medical Services again came under fire in Parliament and, as a result of the recommendations of a Royal Commission, instruction in military hygiene, pathology, and medical administration, and subsequently in clinical medicine, was gradually transferred to London. With the opening of the Queen Alexandra Military Hospital on the east side of the Tate Gallery in May, 1905, the Army Medical School at Netley finally closed. During this period at Netley no fewer than 3,218 surgeons were trained. Initially, the School was accommodated in the laboratories of the Royal College of Surgeons on the Victoria Embankment, but in 1907 the College was opened on its present site on the west side of the Tate Gallery. In 1908 the College was admitted as a school of the University of London in the Faculty of Medicine. During the first world war the College continued as a research establishment and centre for vaccine production. The first prototype respirator against poison gases was designed and tested there. Between the wars routine instruction was resumed and medical research undertaken, and since the end of the second world war the field has been further expanded. The College is now recognized as a teaching centre for the diploma in tropical medicine and hygiene, and special courses are run for specialists in Army health and pathology. In addition assistance is given to officers studying for higher degrees in medicine and surgery.

Centenary Celebrations

The ceremony began with the march of the Royal Guard of Honour, provided by the Royal Army Medical Corps and preceded by the Corps staff band, from the Queen Alexandra Military Hospital to the parade ground at Millbank Barracks. There, after the representative colonel commandant, Royal Army Medical Corps, Major-General D. Bluett, had been presented to Her Majesty Queen Elizabeth the Queen Mother by the D.G.M.S., Lieutenant-General Sir Alexander Drummond, the Queen Mother received a Royal Salute and inspected her Guard of Honour (Fig. 1). The Secretary of State for War, Mr. John Profumo, then presented members of the Army Council and the Army Medical Advisory Board—Lord Moran, Dr. E. R. Boland, Sir Arthur Porritt, Dr. E. R. Cullinan, and Professor J. Bruce, and their wives. The Director-General presented Major-General W. D. Hughes, commandant of the Royal Army Medical College, and Her Majesty entered the College, where she met other senior officers of the Army Medical, Dental, and Nursing Services.

A large company assembled in the College's lecture theatre, where after a fanfare of trumpets, the National Anthem, and prayers, the Secretary of State gave an address in which he welcomed the Queen Mother and outlined the history of the College. Sir Arthur Porritt, president of the Royal College of Surgeons, then requested Her Majesty to present the Mitchiner medals for 1959 and 1960, respectively, to Lieutenant-Colonel I. A. Walsh and Major-General W. D. Hughes. Dr. E. R. Cullinan, honorary consulting physician to the Army, asked her to present to Professor John Bruce the McCombe lecture-professorship of military surgery, and Dr. E. R. Boland, president of the United Services Section of the Royal Society of Medicine, asked her to present the Guthrie Award to Sir Stanford Cade (Fig. 2). Major-General W. D. Hughes then invited her to present the College prizes.

Chair of Military Surgery and R.C.S.

After the prize-giving, the president of the Royal College of Surgeons announced the approval, in principle, of a proposal that the historic professorship of military surgery at the Royal Army Medical College should be brought under the aegis of the Royal College of Surgeons. A committee had been set up to consider how best this might be done.

The Queen Mother then spoke. In a short but inspiring address she expressed her pleasure at being present on this occasion of the celebration of great achievement. She thought that even Florence Nightingale could never have foreseen the progress that had been made. She was especially satisfied to contemplate the links which had been established by interchange of students from many Commonwealth countries and was delighted to learn that the professorship of military surgery was to come under the aegis of the Royal College of Surgeons, of which she was so proud to be a Fellow. After she had been thanked by the Director-General Army Medical Services, the Queen Mother visited the Army Health Laboratory and the College Library, where she met senior officers of the Medical Services of the Royal Navy, the Royal Air Force, of Commonwealth, N.A.T.O., C.E.N.T.O., A.F.N.E., and S.E.A.T.O. nations, and of the Sudanese and Yugoslavian Army Medical Services. She then had tea in the Officers' Mess, and concluded her visit by inspecting the Victoria Cross Room.

THIRD EUROPEAN CONGRESS OF CARDIOLOGY

[FROM A SPECIAL CORRESPONDENT]

The Third European Congress of Cardiology was held in Rome from September 18 to 24, under the presidency of Professor LUIGI CONDORELLI. It was attended by well over a thousand delegates from all countries of Europe and by representatives from America, Canada, Australia, Africa, Egypt, and Israel, including Professor Ignatio Chavez, president of the International Society of Cardiology, Dr. Paul White, its honorary president, and Dr. Kempson Maddox, president of the Asian-Pacific Society of Cardiology. Dr. Evan Bedford, president of the European Society of Cardiology, led the British delegation of 63 members, who presented 29 communications.

The opening ceremony took place in the Aula Magna of the University, and the scientific sessions were held in the

spacious Palazzo dei Congressi, where a simultaneous translation service into English, French, German, and Italian was provided in all auditoria. Plenary sessions were held in the mornings and were devoted to symposia or conferences, with invited speakers, on topics of special interest. These included cardiomyopathies, vector-cardiography, coronary circulation, ultra-microscopy and cyto-chemistry of the myocardium, radio-isotope and dye-dilution techniques, cardio-respiratory insufficiency, and the aetiology of congenital heart disease. Formal lectures were given by Dr. Evan Bedford, Professor Lenègre, and Professor Condorelli. In the afternoons, 320 communications were given.

Professor LENÈGRE, reviewing current problems, said that the cardiologist's role included practice, teaching, research, and administration, and that in addition he was faced with a plethora of scientific meetings, congresses, special journals, lengthy papers, and the incessant introduction of increasingly complicated diagnostic techniques. To keep pace with this might demand a universal intelligence and great resistance to fatigue. He envisaged the need for some sort of restrictive measures in future, and perhaps a basic international textbook covering the essentials of cardiology for the practising doctor. Dr. EVAN BEDFORD emphasized the increasing tempo of advancing knowledge to-day compared with the past, which made it difficult to orientate ourselves correctly. He cited some lessons from history as providing guidance in this respect.

Dr. HEIM DE BALSAC believed that the combination of extra-corporeal circulation with deep hypothermia represented a great advance in open heart-surgery. Dr. DUBOST described the technical details of this method, which he advocated for all lengthy and intricate intra-cardiac operations, and he envisaged its application to the surgical treatment of coronary disease.

Social events included a reception on the Capitoline Hill, visits to various museums, a banquet at the Palazzo Venezia, and a ball at the Palazzo Barberini. Delegates and their wives were received at a Papal Audience in the Vatican on the final afternoon.

Recommendations on the design and use of protective clothing for aircraft-crash workers are discussed in a Fire Research special report, *Protective Clothing Against Flames and Heat*. The recommendations are based on laboratory tests devised and carried out by the Joint Fire Research Organization to assess the protection afforded against flames and heat by many types of clothing, and are applicable, in addition, to protective clothing for workers in industries involving high-temperature processes. The report analyses conditions of air temperature and radiant heat which firemen and some industrial workers may encounter. It continues by discussing in simple terms the effect of heat on the human body as well as the limits of tolerance, and, finally, explains the ways in which suitable protective clothing can give protection against differing conditions of air temperature and radiant heat. Thus, for example, the intensity of thermal radiation encountered by a rescue worker at an aircraft-crash fire may be about 0.5 calories per square centimetre per second. Radiation at this intensity falling on unexposed skin could cause unbearable pain in under two seconds, but clothing with a suitable reflecting outer surface could afford protection for a matter of minutes without undue discomfort. Contact with flames, however, would rapidly destroy the reflecting power of the surface, and in these conditions it is necessary that the insulation of the garment and its ability to store heat should be sufficient to give adequate protection. There are short notes as well on special requirements for protection for the head, hands, and feet and methods of obtaining protection for long periods by artificially cooling the clothing externally. (*Fire Research Special Report No. 3*, published for D.S.I.R. and Fire Offices Committee Joint Fire Research Organization by H.M.S.O., price 3s., by post 3s. 4d.)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Faecal Incontinence in Children

SIR,—The careful study from Cambridge (October 22, p. 1175) of the common, distressing, and so frequently misunderstood symptom of soiling in childhood will arouse much interest and probably some controversy.

In a series of 67 cases studied in my department the most striking fact that emerged was that the average duration of symptoms before the child arrived at the clinic was three and a half years. Most of the children were cases of faecal impaction and overflow incontinence, and were relieved by enemas, aperients, and re-education, but we did not think it possible with this long history to know at what point on the psychosomatic vicious circle the trouble originally began.

We would regard as mainly somatic those cases in whom structural disease can be demonstrated, this to be suspected when there is a history of constipation in infancy, and as mainly psychic those in which soiling occurs in the absence of either structural disease or faecal impaction. This in our series leaves about three-quarters of the cases in which "psychic and somatic factors are so interwoven that neither can be ascribed a primary role."

The authors of this paper say that their rather rigid division of cases is unfashionable. One can imagine Procrustes himself making the same cautious admission, and I would go further and say that such a division depends too much on the attitude of the observer to be really tenable. I would suggest, too, that it is wiser and safer on the whole to assume that all these unfortunate children need both paediatric and psychiatric help, and that this is best provided in concert.—I am, etc.,

Reading. J. J. KEMPTON.

SIR,—Some comment is called for on the interesting paper by Drs. Marian Coekin and Douglas Gairdner (October 22, p. 1175) in which these authors divide their cases of faecal incontinence into mechanical and psychogenic. No exception can be taken to the view that constipation may proceed onwards to incontinence, but only to the mechanistic theory of the origin of the constipation itself in the larger of their two groups and to the idea that this is the cause of pot-refusal. Details of toilet-training and the child's reaction thereto have been omitted from their paper except in so far as "pot-refusal" is regarded as an effort to pass a constipated stool in the least uncomfortable manner. However, it should be noted that children who defaecate standing up or lying down with extended legs do so, not because they find it easier this way but because these positions are precisely those adopted in trying, however unsuccessfully, to prevent a motion passing, and this is a very common observation in those who resist potting.

Where we differ is as to which comes first as a rule—constipation or pot-refusal—a difference in emphasis rather than of fact. Only 27% of the authors' cases of primary constipation were constipated in the first six months of life, a figure which properly should be compared with the vast numbers of controls who, for reasons of underfeeding

or infection, may have become constipated, a few among them developing an anal fissure as a result. Infants with an anal fissure rarely become incontinent in later years, but this may be due to early treatment. Moreover, in a hitherto unpublished series of 266 cases of encopresis, 166 of them since birth, only 17 had a history suggestive of anal fissure, and from the age at which rectal bleeding was first noticed it appeared that in most of them the fissure was secondary to "colonic inertia" and an aggravating rather than a causative factor. Most of these cases with an anal fissure were found in a small group of 29 children whose encopresis was acquired, unassociated with enuresis, and in which the sex incidence was parity, unlike that found in the rest of the soilers. But in the whole series primary constipation was deemed to be the sole operative factor in relatively few instances.

There remains the 73% of Coekin and Gairdner's cases in which a history of constipation within the first six months was not obtained. In my series, 89% of the children who were soiling from birth onwards had resisted their toilet-training, in contrast with cases of simple constipation without incontinence who in general complied with their training. Bowel negativism, arising out of personality factors in child and in mother, is so common, therefore, as to suggest cause and effect, and in my view this is the chief operative factor. If bowel negativism is psychogenic, soiling from birth is even more so.

However much our opinions may differ on the aetiology of constipation itself, and consequently on its prevention, our views on treatment are identical. I am certain Drs. Coekin and Gairdner are correct in treating the constipated child by mechanical means, whether the constipation is psychogenic or not. It is necessary to restore the elasticity of the over-distended bowel, but equally one agrees that psychiatric help is needed, especially for the non-constipated child. Both paediatrician and psychiatrist have their roles to play in a manner complementary to one another. It is indeed a pity that in so distressing a condition as faecal incontinence a closer co-operation between the two is not more often forthcoming, and one may hope that this stimulating paper will achieve this very object.—I am, etc.,

London W.1. S. B. DIMSON.

SIR,—I was interested to read Drs. Marian Coekin and Douglas Gairdner's article (October 22, p. 1175) on faecal incontinence in children. In the last three years I have personally treated thirty patients suffering from this condition: of this number, twelve undoubtedly fall into the group of retention-overflow incontinence, in which "constipation" is an important factor. In these patients I do not consider constipation to be primarily a mechanical problem. In all these patients the faecal incontinence was but one symptom of many, and all showed other retentive phenomena.

Such a patient is Case 1 described by Drs. Coekin and Gairdner, who is still under my care. When first referred he was a very withdrawn depressed child who seldom spoke and showed marked dyslalia; he suffered from insomnia and nightmares, and had periods when he became anorexial. His mother dated the onset of his soiling to when he first started school, which coincided with the birth of a sibling. When first examined he was experiencing intense anxiety over leaving mother to go to school, and at school was described as sensitive and withdrawn. During treatment it became apparent that his retention, not only anally, but orally, was highly emotionally significant for both himself and his mother. His mother was aware of this and found his "unproductiveness" intolerable; her own psychopathology was intricately interwoven with the patient's symptoms. During the first 12 months of treatment the patient was a poor attender: his mother found it difficult to modify her attitudes to him. She felt that his failure to "perform" on the pot could only be dealt with by forcing, and could not tolerate therapy which was directed towards allowing the child freedom, and away from his bowels and his constipation.

At the mother's request the case was reviewed by my paediatric colleagues and it was decided that physical methods should be reinstituted *in conjunction with the continuance of psychotherapy*. For a period following physical treatment the child ceased to soil, but he became constipated again and has since started soiling again. At present he is now soiling freely, but it is no longer a retention overflow. His speech is more spontaneous, he is no longer depressed, and is able to express his resentments much more openly and normally. His mother can now tolerate the absence of physical treatment, and during the last six months the child has had no enemas.

In my opinion there are cases of faecal incontinence where the withholding of physical methods of treatment may defeat the psychological aims. It is necessary to have a close liaison between paediatric and psychiatric departments—a dogmatic approach by either specialty does not help the patient, and treatment must be directed towards the patient's needs, not the doctor's.—I am, etc.,

Addenbrooke's Hospital, Cambridge. B. F. WHITEHEAD.

SIR,—Drs. Marian Coekin and Douglas Gairdner's article (October 22, p. 1175) helps to simplify the approach to this troublesome condition. A warning is, however, called for in the use of enemas in children with chronic constipation. Cases of water intoxication induced by tap-water enemas are probably commoner than is realized.[1] The symptoms include vomiting, pallor, polyuria, convulsions, and coma. Death may ensue in severe cases[2 3] unless energetic measures are taken. Specific treatment consists in intravenous hypertonic saline to re-establish isotonicity and electrolyte balance. Normal saline would seem to be the vehicle of choice for enemas in children; as an added safeguard, the amount of fluid should be limited and every effort made to retrieve it.

There can be little justification for running 1 to 2 litres of contrast medium into the lower bowel of a child. Water can be absorbed in a surprisingly short time from a large bowel, which, due to chronic constipation and dilatation, presents a much increased absorptive surface. The authors point out that radiological investigations add little to what can be learned clinically and are being increasingly little used. If radiological investigation is required, the requisite information can usually be obtained by the use of only a small amount of barium, the flow being observed with the child in different positions.—I am, etc.,

The Royal Infirmary, Huddersfield. W. P. SWEETNAM.

REFERENCES
1 Ziskind, A., and Gellis, S. S., *Amer. J. Dis. Child.*, 1958, **96**, 699.
2 Jolleys, A., *Brit. med. J.*, 1952, **1**, 692.
3 Sweetnam, W. P., ibid., 1952, **1**, 866.

Leukaemia and Prenatal *X*-rays

SIR,—A recent follow-up of 39,166 children who were *x*-rayed *in utero* produced 9 cases of leukaemia when, even if prenatal *x*-rays carried no risk of this disease, between 10 and 11 cases were expected.[1] At first sight these prospective data were more suitable for testing the effects of prenatal *x*-rays than the retrospective data which first suggested that such exposures increased

the risk of leukaemia and cancer[2]; at least they are free from the suspicion that mothers of live children are less reliable witnesses than mothers of dead children.

There are, however, several reasons why the children included in the recent survey are unlikely to be typical of all children *x*-rayed *in utero*. All we know at present is that they were born in eight hospitals in Edinburgh and London some time between 1945 and 1957; that their names were checked with the names of children who died of leukaemia between 1945 and 1958, and that children *x*-rayed elsewhere than in the hospitals where they were born were not included. It is important to know the following additional facts: (1) what numbers of children were born in each successive year and what proportion were first-born children, (2) what were the expected and observed numbers of leukaemia deaths among the first-born and later-born children in each year.

It has already been shown that leukaemia risks for first-born children differ from those of later-born children,[3] the former having a greater chance of developing lymphatic and stem-cell leukaemias during the peak incidence years (2–4 years). There are also some unpublished data, presented at the September meeting of the Society for Social Medicine, which suggest, first, that the early peak of leukaemia mortality is produced by lesions which predate conception and result in so-called lymphatic or stem-cell leukaemias (prezygotic leukaemias); secondly, that relatively more first-born children suffer from these lesions than later-born children; thirdly, that the maximum incidence of leukaemias and cancers due to prenatal *x*-rays occurs, not between 2 and 4 years, but between 6 and 9 years.

It is possible that the close correspondence between the observed and expected numbers of leukaemia deaths reported by Drs. Court Brown and Doll is due to a deficiency in certain cohorts and an excess in others. This is one of the facts we need to know, for if there is a significant deficiency in the younger cohorts it would raise the suspicion that some leukaemias were missed; a suspicion which is already aroused by the fact that only two girls were found among the leukaemia deaths, compared with seven boys.

No doubt the authors of the recent report have considered all these points and will eventually publish their data in full. The point I want to make is that the children included in this survey were probably biased in favour of children who are not suitable for studying the effects of prenatal *x*-rays—that is, first-born children under 6 years of age. Also any survey which is confined to eight hospitals in two cities runs a risk of producing misleading results. If children from several hospitals in different parts of the country had been included in the survey it might have been possible to collect a large group of children who were either *x*-rayed in the first half of pregnancy or had had several prenatal exposures. If such a group had failed to reveal an excess of leukaemia and cancer deaths, there would have been good reason to suspect the Oxford data. But if, as I suspect, most of the children were first-born children and were still under the age of 6 years at the time of the follow-up, it will be wise not to draw far-reaching conclusions until we know how many of them have died of leukaemia or cancer by 1965, the first year when all the children will have passed their ninth birthday.—I am, etc.,

Department of Social Medicine, Oxford University. ALICE STEWART.

REFERENCES

[1] Court Brown, W. M., and Doll, R., *Proc. roy. Soc. Med.*, 1960, 53, 761.

[2] Stewart, A., Webb, J., and Hewitt, D., *Brit. med. J.*, 1958, 1, 1495.

B.C.G. Vaccination

SIR,—I would like to congratulate Dr. Margaret I. Griffiths on her excellent report on the "Multiple-puncture Vaccination in the Newborn with Freeze-dried B.C.G. Vaccine" (October 15, p. 1116). Dr. Griffiths has given much thought to modifications of guns and needles and has devised a method of vaccination which gives a very satisfactory conversion-rate within four weeks of vaccination. The report covers the vaccination of 2,221 newborn. Under our scheme in Dublin city approximately 6,000 newborn are vaccinated each year with Danish liquid vaccine, using the intradermal method, and the vaccinations are made only by the medical staff. With the present modified strength of the Danish liquid vaccine, complications such as axillary adenitis are rare nowadays, and the complication rate is considerably less than in the earlier years—the few which occur yield readily to treatment.

The multiple-puncture method appears more time-consuming, as following each vaccination the base-plate requires to be immersed in the ether–alcohol mixture described for not less than 30 seconds. The possibility of human error in curtailing this immersion time appears to equal the possibility of making too deep an injection in the rush of a busy clinic. I think Dr. Griffiths has made a very valuable contribution to B.C.G. work in this report, but with the exception of the more rapid conversion-time achieved the advantage of the multiple-puncture method does not appear outstanding. The follow-up of multiple-puncture vaccinations in five years' time will be of interest.

Dr. K. Neville Irvine's article in the same issue (p. 1119) is of special interest, as he stresses the elimination of routine post-vaccinal testing. I agree with his observation that the presence and size of the local reaction following Danish liquid vaccine serves as an index of successful vaccination. He considers that only those with no local reaction require a conversion test. In Dublin we have for some time limited post-vaccinal testing to contacts, and to those who show little or no local reaction at the vaccination site. Otherwise, post-vaccinal testing is not routine, except sample testing as a check in the efficiency of the vaccine. In the newborn group, the infants are seen three months after vaccination, mainly to observe any possible complication and to record the size of the vaccination nodes. The omission of the post-vaccinal test saves the mother an unnecessary visit for the reading of this test, and from an administrative viewpoint prevents overcrowding at the clinics. I congratulate Dr. Irvine on his valuable paper and I agree that, with experience gained over the past twelve years, inspection of the nodes is sufficient in the majority of cases.—I am, etc.,

B.C.G. Section, Dublin Health Authority. M. DUNLEVY.

False-positives with "Phenistix"

SIR,—A recent trial was carried out at Digby Section of Digby-Wonford Hospital, using "phenistix" (a strip impregnated with a mixture of ferric ammonium sulphate, magnesium sulphate, and cyclohexylsulphamic acid) for the detection of phenylketonuria. The subjects were ten adult male patients, suffering from mental subnormality (mental defect) and the test was positive in four (40%), the quantitative reading in each case being 15 mg. A confirmatory test using ferric chloride was carried out on each patient of the series at the Pathological Department, Royal Devon and Exeter

Hospital, and in no case was a positive result obtained. This suggests a high incidence of false-positive reactions in this admittedly small series.

Of the patients tested and who gave a positive reaction, three were receiving chlorpromazine, and one patient was not receiving any medication. Of those giving a negative reaction, the following conditions pertained: one patient received perphenazine, one a barbiturate, one an anticonvulsant, one "pentoxylin" (rauwiloid), and one patient received no medication. There was no alteration in the patients' medication before or during the trial.

In view of the above results, it appears that large-scale testing is necessary to confirm the validity of the phenistix method of testing for phenylketonuria.

My thanks are due to Dr. Lewis Couper, medical superintendent, Digby-Wonford Hospital, for his interest and great help in carrying out the investigation, and to Dr. J. Edgcumbe, consultant pathologist, Royal Devon and Exeter Hospital, who carried out the urine analysis.

—I am, etc.,

C. P. O'TOOLE.

Digby Hospital, Exeter.

Cycloserine in Urinary Infections

SIR,—We have read with interest the report of Drs. R. W. Fairbrother and G. Garrett on the treatment of urinary infections with cycloserine (October 22, p. 1191). The conclusions which are drawn from their experience in the treatment of 22 patients, of whom no fewer than 17 were complicated by neurological or anatomical disorders, are surely not applicable to the majority of patients seen either in general or hospital practice. It is well recognized that *E. coli* is the commonest single infecting organism in uncomplicated urinary-tract infections, yet it was only present in a minority of the cases treated by these authors. It would be unreasonable to expect full clinical and bacteriological cure in the complicated cases, no matter which antibiotic or chemotherapeutic agent had been used. The doses of cycloserine employed were not apparently adjusted in relation to the patients' renal function. In these circumstances unduly high blood levels and therefore toxicity were to be anticipated. The duration of treatment averaged seven days. Further, as yet unpublished observations of our own suggest that to obtain lasting clinical and bacteriological cure—established by a minimum follow-up period of one month—a minimum dosage schedule of 250 mg. 8-hourly for 14 days is necessary. This is so, even in uncomplicated cases having normal renal function and infected with cycloserine-sensitive organisms.

Despite the differences between their techniques and ours for determining both organism-sensitivity and urinary drug-concentration we are surprised to note the very high minimum inhibitory concentrations quoted for *E. coli* and also the high concentrations of the drug attained in the urine. Since their determinations were made with reference to "a special salt of cycloserine" the nature of which is not stated, it is tempting to speculate that this substance may possibly differ materially from the "pure" cycloserine (supplied to us by Eli Lilly and Co.) on which our measurements were based. This hypothesis gains some support from the remarkable urinary level of 960 micrograms per millilitre attained in 10 to 22 cases, which would represent 100% recovery of the drug administered if the 24-hour urine volume were 1,040 millilitres, and more than 100% recovery at average urine-output.

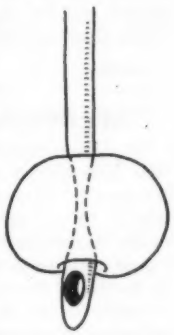
Despite the strictures of Drs. Fairbrother and Garrett we continue to regard cycloserine as a valuable urinary antibiotic where the bacteriological and biochemical evidence suggests that it is likely to be effective in patients having no drainage defect in the urinary tract. We agree, however, that laboratory control of cycloserine therapy is essential in the management of such patients.—We are, etc.,

J. McC. MURDOCH.
S. C. FRAZER.
J. D. SLEIGH.

Departments of Infectious Diseases, Clinical Chemistry, and Bacteriology, University of Edinburgh.

Hazard Associated with Foley Catheters

SIR,—Foley catheters are in common use after such operations as prostatectomy, where free drainage of urine containing blood is essential. If the lotion does not flow freely in and out of an Anard syringe an obstruction is present somewhere in the drainage system, and, unless found and corrected, complete blockage by clots of blood is likely.



In the last few months I have encountered a new cause of obstruction occurring in the catheter, but only after it has been inflated. If the strengths of the rubber of the catheter and of the balloon are ill-adjusted by the manufacturer, inflation of the balloon collapses the catheter within it to a flattened slit (see diagram), causing the obstruction mentioned above. Once this is understood its occurrence is easily detected by the rapid inward and the slow outward flow on irrigation. Changing the catheter is the only remedy.

—I am, etc.,

J. A. CARR.

Greenmount, Lancs.

Drug-induced Gout

SIR,—It was with great interest I read the account (September 17, p. 832) of "Hyperuricaemia Related to the Treatment of Hypertension" by the Hammersmith group. May I give my own experience of using bendroflumethiazide, which is in accord with the conclusions of this paper?

A short while ago I took over the treatment of a hypertensive with a long history of gout, but with few actual acute episodes to his record. I started him off on reserpine 0.25 mg. t.d.s., as he had had little medical treatment before this. He did well, but I thought I would try and get the diastolic a little lower, and added bendroflumethiazide 2.5 mg. b.d. to his reserpine. Within two weeks he had started the worst attack of gout he had ever had. His blood uric acid was 4.9 mg./100 ml.

On checking the aetiology of gout in Cecil and Loeb's *Textbook of Medicine*,[1] and seeing that Professor Hench included mercurial diuretics as a possible precipitating cause, I thought perhaps oral diuretics might have the same effect. I then took the patient off the bendroflumethiazide, and he soon recovered on colchicine. It was therefore with especial interest I read this article, and it was a pleasure to find my

clinical impressions supported by Hammersmith's scientific survey. I hope this subject will be pursued further by those with extensive laboratory facilities.—I am, etc.,

Mqanduli, Transkei, South Africa. PETER LANE.

REFERENCE

[1] Hench, P. S., in *A Textbook of Medicine*, 1959, ed. R. L. Cecil and R. F. Loeb, 10th ed., p. 597. Saunders, Philadelphia and London.

Hypernephroma and Polycythaemia

SIR,—I was interested in the paper by Dr. A. Drivsholm on hypernephroma and polycythaemia (October 8, p. 1063). For several years a similar case in which the polycythaemia appears to have antedated the renal changes, which were initially those of hydronephrosis on one side, has been under my observation. Latterly there has been no dubiety about the diagnosis, and it has unfortunately been associated with metastases. In view of the relative rarity of the condition, as was pointed out by the author, I felt that I should draw to his attention this further case.—I am, etc.,

Inverness. J. RONALD.

Megaloblastic Erythropoiesis in Pregnancy

SIR,—The paper of Dr. Alexander McKenzie and Miss Joy Abbott on "Megaloblastic Erythropoiesis in Pregnancy" (October 15, p. 1114) was of particular interest to us, because the incidence of this condition at the Sunderland Maternity Hospital (1 case in 26.6 deliveries) agrees remarkably with the figure reported by us from the National Maternity Hospital, Dublin (1 case in 24 deliveries).[1] We also found a high incidence of the condition in twin pregnancies; in fact 7 of our 95 cases were twin pregnancies. In our series of 95 cases, accidental haemorrhage was observed in 13 cases (14%). The hospital figure for accidental haemorrhage over the same period of time was 2.5%. We feel that this association is not fortuitous, and it is now our policy to investigate all cases of accidental haemorrhage for evidence of megaloblastic erythropoiesis. In fact in two of our cases the occurrence of accidental haemorrhage led to marrow puncture and the correct diagnosis, although the haemoglobin level exceeded 12 g.

Finally, we were pleased to note that Dr. McKenzie and Miss Abbott had entitled their paper "Megaloblastic Erythropoiesis in Pregnancy" because, as we pointed out in our communication, the term megaloblastic anaemia is hardly a fair one to use with haemoglobin levels of 12 g. or over. We suggested that "the term megaloblastic erythropoiesis of pregnancy should be used to refer to patients with haemoglobin levels of 12.1 g. or more who show a megaloblastic marrow reaction."—We are, etc.,

M. I. DRURY.
National Maternity Hospital, Dublin C.5. CHARLES V. COYLE.

REFERENCE

[1] Hourihane, B., Coyle, C. V., and Drury, M. I., *J. Irish med. Ass.*, 1960, 47, 1.

Personal Record Cards

SIR,—Dr. John Riddell (October 22, p. 1239) is to be congratulated upon having examined the use of personal record cards of immunization with a critical eye. But one may perhaps take issue with him on the conclusions to be drawn from his findings. Two years after immunization he found that the record was unavailable or inaccurate in 47% of children, and he draws the conclusion that personal record cards are not a satisfactory method of dealing with the problem. However, it is noted that 253 children had not in fact been issued with a record card at the time of immunization. Of the 1,343 children to whom cards had been issued, an accurate record was apparently available two years later in 853, or nearly two-thirds. Dr. Riddell would be justified in regarding this degree of success with some satisfaction. The rate at which prophylactic tetanus antitoxin is given is such that, if a record had been available for a similar period of time after immunization in two-thirds of all children in the country, several thousands of injections of antitoxin could have been prevented. This would surely be an encouraging beginning. If we were to inform parents more widely of the reasons why it is important to keep the record we might well see an improvement. Until a better method of keeping personal records is available it would be a great pity to abandon the personal record card merely because it is not perfect.—I am, etc.,

Public Health Department, The County Hall, London S.E.1. IAN TAYLOR.

Doctors' Letters

SIR,—From this distance I have been following the correspondence in the *B.M.J.* concerning the size of medical record envelopes and hospital letters. As far as military practice is concerned in this area, all specialists commence their letters with a true copy of the M.O.'s letter which accompanied the patient to hospital. Then follows the hospital case history with results of special investigations, etc. The comparisons between the two are interesting and in some cases embarrassing. As far as I know this is not carried out in civilian practice, but would be an appreciated and helpful service to the G.P. at home. The extra cost would be nil and would probably lead to an increase in the standard of doctors' letters.—I am, etc.,

Ipoh, Malaya. W. D. PYLE.

Health Services in Rhodesia and Nyasaland

SIR,—In view of your emphasis on the opinion of members of the Monckton Commission from within the Federation and the figures you cite (October 22, p. 1213) may I mention that there were 13 such members; that three of these "have reached the conclusion that health must be a Territorial subject" (p. 51); that two "welcome the proposals to make . . . health . . . Territorial responsibilities" (p 152); and that three "agree with the majority of the members of the Commission that the Territorial Governments should have the ultimate right to take over the administration of this function should they so desire"? Of these eight members four are African.

Referring to the Commission's recommendation that the Territorial Governments negotiate the setting up of a Central African Health Service, the dissentient note, supported by the other five members from within the Federation, in your words, "pertinently asks in what way this proposal differs from an effort to reform the Federal Service," and then points out the difference it objects to. Other differences are: (1) that the territories and peoples, by having more direct

responsibility and commitment, may be more identified with the service and more constructive towards it, particularly those less identified at present with the Federation ; (2) assuming that the Service, as the Commission suggests, receives assistance from the Federation and that it is in its interest for the Federation to continue, its outside existence, by acting as a support or buttress to the Federation, might contribute more to its stability than if it were incorporated into its structure ; and (3) it could exist without the Federation or be salvaged from it. In any case these five dissentient members recommend as an objective " the setting up of a permanent body representative of all four Governments in which will rest responsibility for the administration of all health matters."—I am, etc.,

Epsom. W. M. MCINTYRE.

Haemopericardium During Anticoagulant Therapy

SIR,—Dr. E. E. Okafor (October 15, p. 1159) describes an interesting and instructive patient who developed haemopericardium during anticoagulant therapy. There appear to be two possible explanations. Assuming that an initial myocardial infarction did occur, the patient may then have developed the " post-myocardial infarction syndrome " described by Dressler[1] in 1956. This is characterized by generalized pericarditis, sometimes associated with pleural effusion and pneumonitis, usually appearing 2 to 4 weeks after myocardial infarction. This syndrome may represent a non-specific reaction to the products of myocardial necrosis. As in other forms of generalized pericarditis, anticoagulants are contraindicated and fatal haemopericardium has occurred when anticoagulants have been continued or recommenced on the grounds of recurrent myocardial infarction.

A similar syndrome of pericarditis and pleural effusion sometimes follows heart operations—the " post-cardiotomy syndrome."[2] We have recently had a patient in this hospital in whom dangerous haemopericardium occurred when anticoagulants were given in the presence of the " post-cardiotomy syndrome." This patient will be reported in more detail elsewhere.

Dr. Okafor's patient may have had acute " idiopathic benign " pericarditis *ab initio*. Haemorrhagic pericardial effusion is not unusual in this condition and massive haemopericardium has sometimes followed the use of anticoagulant drugs. Dr. Okafor's experience again emphasizes the grave dangers of anticoagulants in generalized pericarditis.—I am, etc.,

Sully Hospital, Penarth. WILLIAM G. SMITH.

REFERENCES
[1] Dressler, W., *J. Amer. med. Ass.*, 1956, **160**, 1379.
[2] Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, T. J. E., and Glover, R. P., *Circulation*, 1953, **8**, 481.

" Persantin " in Coronary Disease

SIR,—In your issue of September 17 (p. 835) Drs. T. Foulds and J. Mackinnon published their results with " persantin " and concluded that the effect of the preparation did not differ from that of a placebo. We have just completed a similar double-blind trial with persantin in cases of angina pectoris.

Eleven patients were treated for 12 weeks. The dosage was 25 mg. three times a day with a tablet of lactose indentical in appearance as a control. Each substance was given for six weeks. One patient died during the trial and two patients did not report for assessment. Two patients were improved by persantin alone, one of them was worse when given placebo. Two patients were improved by both persantin and placebo. Three patients felt no change at all during treatment with either persantin or placebo, and one patient had more pains when given persantin.

We can thus confirm that persantin in a controlled blind trial does not give significantly better results than a placebo tablet.—We are, etc.,

JOHANNES MOSBECH.
PREBEN OLLENDORFF.

Medical Department E,
Frederiksberg Hospital,
Copenhagen, Denmark.

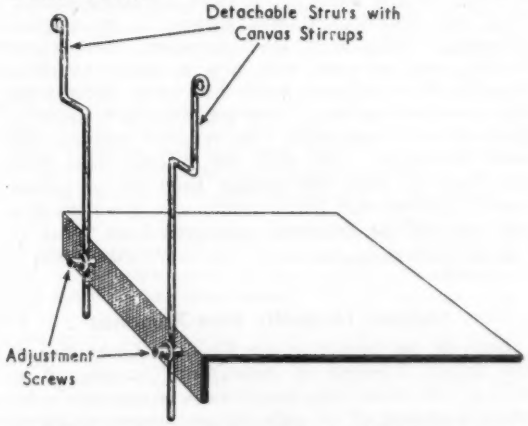
Potassium Perchlorate in Thyrotoxicosis

SIR,—The letter from Drs. M. E. Morgans and W. R. Trotter (October 8, p. 1086) was of special interest to me. At the West London Hospital Endocrine Clinic we began to use this drug soon after reading the first paper in this country on the subject by Drs. Morgans and Trotter. It so happens that our initial and usually maximum dose has been 800 mg. daily, as they now recommend. With an experience of over 100 patients we are glad to say that we have encountered no toxic effects of any significance. We have seen no rash, fever, or adenopathy. It is true that some patients are not fully controlled on this dose, and we have then added a small dose of carbimazole, 5–10 mg. daily.—I am, etc.,

London W.1. L. P. E. LAURENT.

" Obstetric Helper "

SIR,—Drs. P. R. Boucher and Margaret J. Turpin (October 15, p. 1157) are incorrect when they state that there is no satisfactory lithotomy support for domiciliary use. For some years I have been using a portable lithotomy frame (see diagram). This is a more robust modification of the one originally described by Handfield-Jones.[1] Brief reference was made to the frame in a previous letter[2] and produces conditions almost as adequate as those obtained in a labour ward, the only disadvantage being the height of the bed found in the average patient's house, which is unavoidable.



While the " helper " described by Drs. Boucher and Turpin is a marked improvement on the existing straps its efficiency depends on having a relaxed patient and is virtually useless if the patient is at all restless.

I have used the frame for all cases, including forceps, emergency breech deliveries, manual removal of placentas, and repairing perineums. Measuring

2 ft. 6 in. (0.76 m.) by 1 ft. 9 in. (0.53 m.) it is made of aluminium-coated steel and fits almost all cars from a Morris Minor upwards.—I am, etc.,

Liverpool 18. MERVYN GOODMAN.

REFERENCES

[1] Handfield-Jones, R. P. C., *Lancet*, 1956, **2**, 498.
[2] Goodman, M., *Brit. med. J.*, 1957, **2**, 1493.

Marksmanship and Crossed Laterality

SIR,—I have personal experience of the truth of Dr. B. S. Phillips's opinion on this matter (October 22, p. 1239). Although right-handed, I have a dominant left eye. This was first diagnosed, after the firing of one shot, by an elderly instructor at a shooting school in Taunton. It was later confirmed by the ophthalmic department of the Royal Devon and Exeter Hospital. Since that time I have shot with one eye closed and with rather more success.—I am, etc.,

Cheltenham. R. MERRYWEATHER.

SIR,—With reference to Dr. B. S. Phillips's letter (October 22, p. 1239), I described in a letter a simple test for handedness,[1] inspired by a book on shooting, and it may be useful to know that a simple mask which fits on the barrels of a 12-bore shotgun was obtainable from Messrs. Cogswell and Harrison Ltd., of Piccadilly, London W.1. This mask blocked the sighting line of the contralateral eye, and proved satisfactory, closure of the eye being unnecessary.—I am, etc.,

Manchester Royal Infirmary, Manchester 13. MAURICE BIRKBECK.

REFERENCES

[1] *Brit. med. J.*, 1957, **1**, 703.

Nits at the Hairdresser's

SIR,—I wonder if Dr. J. K. Waterlow (October 15, p. 1164) is correct in his assumption that the brushes used in the hairdresser's shop with which he was concerned were in fact infected in the shop, or that the nits were those of the human head-louse.

A number of years ago I was asked to inspect a consignment of hairbrushes which had just been delivered to the stores of a large approved school. Each was unused and still packed in its original wrapping. With very few exceptions the natural bristles were infested with nits in great numbers. Samples of the brushes which had come direct from the factory to the school were submitted to a bacteriologist of wide experience. He reported that the nits were non-viable, and that the brushes had been manufactured from the natural hairs of an animal heavily infested with lice, a condition which then was, and may still be, relatively common.—I am, etc.,

Public Health Department, Cardiff. C. W. ANDERSON.

Sickness Incapacity from Bronchitis

SIR,—In our report to the Research Committee of the British Tuberculosis Association (January 30, p. 297) it was stated that bronchitis was responsible for about a quarter of all male sickness incapacity during 1955–6. It has been brought to our notice that this is incorrect, the true figure being about an eighth. Non-tuberculous respiratory disease as a whole caused about a quarter of such days lost, bronchitis accounting for about half of these.—We are, etc.,

R. S. FRANCIS.
New Barnet, Herts. C. C. SPICER.

Obituary

C. E. WOODROW, M.B., B.Ch., M.R.C.P.

Dr. C. E. Woodrow, who had practised in Scarborough for over thirty years and was consultant physician to the Scarborough and district group of hospitals, died suddenly at home on October 15. He was 59 years of age.

Cyril Erskine Woodrow was born on October 2, 1901. He had a brilliant academic career, winning a scholarship to Caius College Cambridge, and taking first-class honours in both parts of the National Sciences Tripos. He held a Tancred studentship (for eight years) at Cambridge and at St. Bartholomew's Hospital, where he completed his clinical training. Qualifying in 1927, he graduated M.B., Ch.B. and took the M.R.C.P. in 1929. After holding the post of house-physician at Bart's he became resident medical officer at the Hospital for Epilepsy and Paralysis, Maida Vale.

In 1928 he joined a practice in Scarborough, and seven years later was appointed honorary consultant physician to the Scarborough Hospital. As honorary secretary of the Scarborough Division of the B.M.A. from 1939 to 1949 and as chairman in 1950–1 he did much good work, and his colleagues will miss his kindly ways and the help which he gave so readily. He also represented his Division at Annual Meetings from 1944 to 1948.

At the memorial service held on October 21 the church was filled to the doors with his colleagues and patients, and with nurses and first-aid workers, who all came to pay their last respects to one who was greatly admired and respected.

L. S. D. writes: Dr. Woodrow's work was his absorbing interest, and, though keenly interested in sport, he had time only for an occasional round of golf (even so he played down to a 4 handicap). His consolation has been his happy family life. His work and his kindliness will be the treasured memory of his colleagues and his patients alike. Our sympathy goes out to his widow and to his two children who have been so suddenly and prematurely bereaved.

DOROTHY A. PRIMROSE, M.B., Ch.B.

Mrs. D. A. Primrose (née Robertson) died in retirement at Brora, Sutherland, on August 16 at the age of 65.

Dorothy Anderson Robertson was born on April 17, 1895, the daughter of the Rev. James Anderson Robertson, M.B., who forsook a lucrative west-end practice in Glasgow to become a priest in the Episcopal Church, finally becoming rector at Muthill, Perthshire. Her mother, Miss Mary Weir, was matron of the McAlpin Nursing Home in Glasgow before her marriage. After graduating M.B., Ch.B. at Edinburgh in 1918 Dorothy Robertson became a house-surgeon at the Sick Children's Hospital, Glasgow. In 1919 she married Dr. Edward J. Primrose, who was then on the staff of the Glasgow Eye Infirmary, and in 1927 she also joined the staff as a clinical assistant. She rose to be assistant surgeon and retired along with her husband in 1950. They had four sons, three of whom graduated in medicine, one being an ophthalmologist. Their only daughter was a sister at the National Hospital, Queen Square, and married a doctor.

A. M. W. T. writes: Mrs. Primrose was one of those people who manage somehow to do more than one thing at a time. She contrived to bring up her family and continue working at the Glasgow Eye Infirmary, and during the second world war she kept more or less open house to Servicemen in the city. She was truly a great person, friendly and generous to all, kindly to patients, and always charming. She will be remembered for a long time in the Glasgow Eye Infirmary as an example of what one person can achieve. Our sympathy goes to her husband and family.

G. D. McLEAN, M.B., Ch.B.

Dr. Guy D. McLean, who was in practice at Kinloch Rannoch, Perthshire, died suddenly at his home there on September 22, aged 78.

Guy Dalzell McLean graduated M.B., Ch.B at Glasgow in 1912, and after one or two hospital appointments he joined the R.A.M.C. at the outbreak of the first world war. Attaining the rank of major, he served throughout the war, was wounded, mentioned in dispatches, and awarded the Croix de Guerre. After a few years of practice in the north of England he was appointed to the practice at Kinloch Rannoch under the Highland and Islands medical service scheme in 1928, and for 32 years he ministered to the medical needs of that widely scattered and romantic district. His kindly humour and ready wit endeared him to the hearts of his patients, and even in his later years his youthful figure and freshness of mind were a source of pleasure to patients and colleagues alike. He took a keen interest in the social life of the community and was a leader in their various sporting pursuits. A skilled carver in wood, he designed and executed many articles which beautified his home and those of his friends.

His passing will be regretted by a wide circle of friends, and his departure marks the loss of another exponent of the old school of family doctoring.—C. J. S.

A. P. GIBBONS, M.B.

Dr. A. P. Gibbons, who was in practice in the City of London for many years and was a past-Master of the Society of Apothecaries, died at his home at Farnham, Surrey, on September 27. He was 88 years of age.

Arthur Philip Gibbons was born at Wantage, Berkshire, on July 6, 1872, and was educated at Warwick School and the London Hospital, graduating M.B. in 1895. After holding a number of appointments at the London Hospital, including those of house-surgeon and house-physician, he became a ship surgeon. He served in South Africa in 1900–1 as a surgeon-lieutenant in the Rhodesian Field Force, and soon after his return to England he entered general practice in Camberwell, where he was also medical officer to the provident dispensary.

In 1906 he moved to the City of London, where he practised until 1938, when he retired to Farnham. During the first world war he held a temporary commission in the R.A.M.C. and served at a base hospital at Rouen. In London he became surgeon to the City police and medical officer to Lloyd's Bank and, subsequently, to the Bank of England. A member of the Society of Apothecaries of London, he was elected Master in 1935. At Farnham he cultivated many interests, rendering good service to the St. John Ambulance Brigade. During the second world war he served in the Home Guard. In 1941 he was appointed an Officer of the Venerable Order of St. John of Jerusalem.

In 1905 Dr. Gibbons married Miss Constance R. Clement, who died in 1947. He is survived by his son, a solicitor, and two daughters.

B. H. LEES, M.B., B.Ch.

Dr. B. H. Lees, who had practised for many years in Worthing, died in a nursing-home there on October 3, aged 92.

Bernard Hall Lees was born on October 25, 1867, in China, where his parents worked for the London Missionary Society for forty years. He received his medical education at Cambridge University and at St. Mary's Hospital, where his uncle, Dr. David Lees, was on the staff as honorary physician. After graduating M.B., B.Ch. in 1894 he went to Worthing, and practised there for thirty years. For the greater part of his time he worked single-handed, and his practice left him little leisure. His reward was the gratitude and affection of his many patients. He retired many years ago, but up till an attack of cardiac asthma a few weeks ago he had retained a degree of activity remarkable in a man so nearly approaching the age of 93. Hilaire Belloc wrote, "The grace of God is in courtesy," and that courtesy Dr. Lees showed. He is survived by his devoted daughter Laura, the wife of Dr. C. Gibson.

DUNCAN MACLEOD, M.B., Ch.B.

Dr. D. Macleod, for thirty years a general practitioner in Accrington, Lancashire, died at Stornoway in the Isle of Lewis on October 17 at the age of 61.

Duncan Macleod graduated M.B., Ch.B. at Aberdeen University in 1924. After several years of experience of medical practice he came to Accrington in 1928 as partner to the late Dr. George Beaton. Well known to a large circle of friends, patients, and medical colleagues in the East Lancashire area, he was a man of robust personality and ready wit. Kindly, generous, and rich in human qualities, he had a keen sense of good fellowship and excelled at the informal gatherings of his fellow practitioners.

Although a very hard-worked practitioner for most of his life, he found some time for golf, for his social club, and the occasional angling expedition. He retired from the National Health Service in 1952 and carried on in private practice in Accrington until May, 1960. He was held in high esteem by his medical colleagues and friends in the Accrington district, who mourn his loss.—J. M.

Sir HAROLD GILLIES, C.B.E., F.R.C.S.

The obituary of Sir Harold Gillies was published in the *Journal* of September 17 (p. 866).

Mr. DENIS SUGRUE writes from Dublin: The appreciations of Sir Harold Gillies in the *B.M.J.* have been contributed by those of his most distinguished colleagues and protégés in Great Britain. It is with diffidence that I, one of the latest of his trainees, presume to join in the tributes. It was my privilege as registrar at Rooksdown House during those final years when Sir Harold was the senior surgeon there to attend his famous clinics, to receive the benefit of his scrupulous teaching in technique around the "table," and to hear him frequently enunciate his basic principles —as, for example, "Never do to-day what can honourably be put off until to-morrow."

As a junior member of the staff I was deeply impressed by the frequent examples of the great man's kindness, humility, and simplicity, and of his generosity in inviting me from time to time to partake of the warm hospitality of his home. When I returned to practise the specialty in Dublin, Sir Harold continued to take an interest in my career. His written encouragement, as well as personal contact with him, both in Ireland, when he was holidaying here, and in England, was a stimulus to persevere and overcome the inevitable difficulties encountered in establishing a practice in the specialty.

It would be presumptuous of me to add anything to that which has been so ably expressed in the appreciations about his pre-eminence in the specialty he pioneered, and which has been established through his teaching and influence in so many parts of the world, or of his creative genius in the art of plastic surgery which, inevitably, will secure for him a lasting place in the history of medicine. The uniqueness of his personality, the privilege of receiving his training, the kindness of his continuing interest in my career, and the enjoyment of his friendship will remain for me an abiding and affectionate memory.

H. N. STOKOE, B.M., B.Ch.

The obituary of Dr. H. N. Stokoe was printed in the *Journal* of October 1 (p. 1027).

V. J. D. writes: Dr. Nevill Stokoe's sudden death has brought a profound sense of loss to me, as it must to all who knew him. It is difficult to believe that we shall not

see him again, nor derive comfort and strength from his courage, integrity, and skill. As a general practitioner and as an anaesthetist, his work was a compound of technical excellence, sound common sense, and deep humanity. His unassuming manner and gentle wit, no less than his flair for the refinements of modern anaesthesia, made a tranquil place of any operating theatre in which he worked. Few men can have enjoyed, so unreservedly, the respect and affection of his colleagues and patients, and his loss is hard to bear.

We record with great regret the death on October 31, after a long illness, of Lady Thomson, wife of Sir Arthur Thomson, emeritus professor of therapeutics in the University of Birmingham and President of the British Medical Association from 1958 to 1959.

Medical Notes in Parliament

HOSPITAL CASUALTY SERVICES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Earl WINTERTON asked the Government on October 26 for a committee of inquiry to examine the methods for dealing with casualty cases in Health Service hospitals, in view of the criticisms made by an unofficial committee and of other evidence to the same effect. He was reminded by Lord ST. OSWALD that the standing medical advisory committee of the Central Health Services Council had appointed earlier this year a subcommittee under the chairmanship of Sir Harry Platt to consider the organization of hospital casualty and accident services and to make recommendations about their future development. A similar committee had been set up by the Scottish Health Services Council. Lord St. Oswald added, "I have no doubt that these committees will consider the recommendations made in the study, based on 20 casualty departments, which was recently published for the Nuffield Provincial Hospitals Trust."

Earl WINTERTON called attention to a serious indictment of the arrangements for dealing with casualties which had appeared in *The Times* from a responsible writer.* In that case there was a mixture of inhumane and ineffective treatment of a man who had broken his thigh and was suffering from shock. Was the Ministry of Health prepared to take any action in the case, in view of the fact that the answer given by one hospital made no mention of one of the worst features of the treatment—namely, that the patient was refused a cup of tea? Lord ST. OSWALD said that he had not read the account of the case, but promised to see that the subcommittee was informed of it if Earl Winterton would send him the details.

Lord STONHAM commented that, at the instance of the Minister, every regional board had been seriously considering this problem. They were proposing to concentrate major casualty centres in the hospitals in each group, but what was needed was more money to equip, expand, and provide more casualty centres. Would this be forthcoming? Lord ST. OSWALD replied that any decisions of that kind must rest on the findings of the subcommittee, which had been set up specifically for the purpose of discovering what the facts were and of suggesting remedies.

ROYAL ASSENT TO PROFESSIONS SUPPLEMENTARY TO MEDICINE BILL

The Professions Supplementary to Medicine Bill received the Royal Assent on October 27, the last day of the session. The effective amendments conferring subpoena powers on the disciplinary tribunals for these professions, deferred until the Simonds Committee had reported,† were inserted in the House of Lords before the long recess and did not come before the Commons until its reassembly on October 25.

*See "A Cup of No Kindness" from "a Correspondent," *The Times*, September 29, p. 14.

†See *Brit. med. J.*, 1960, **1**, 1666.

The effective words, plus provisions for applying the new rules in Scotland, are an addition to the Second Schedule ("The Investigating and Disciplinary Committees") and state

"In England or Wales or Northern Ireland the Committee may administer oaths, and any party to the proceedings may sue out writs of subpoena ad testificandum and duces tecum, but no person shall be compelled under any such writ to produce any document which he could not be compelled to produce on the trial of an action."

Mr. ENOCH POWELL asked the House to agree with the Lords in this, as his first Parliamentary action as Minister of Health. He based his request on paragraph 40 of the Simonds Report, in which the committee state "that justice can only be done if material evidence is not withheld, that this is true of all courts and tribunals to which the administration of justice is entrusted, that it applies with particular force to tribunals having power to impose such formidable penalties as have the disciplinary tribunals of professional bodies."

Dr. EDITH SUMMERSKILL (Warrington, Lab.) accepted the amendments on behalf of the Opposition. But they did not pass without demur. Lord BALNIEL (Hertford, Con.) expressed some doubt whether these tribunals were really "fitted and equipped to deal with matters of evidence in accordance with established legal principles," in the cautionary words used by the Simonds Committee. They were to have a legal assessor, but a court consisting of a few remedial gymnasts, or chiropodists, or dietitians, with no legal experience apart from the advice it received from its assessor, seemed a weak body to wield these substantial judicial powers. Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) thought these fears exaggerated. Were lawyers the only people to understand evidence? Lay people listening only to cases of this type would often have an advantage over the lawyer because they knew all the antecedent circumstances, the environment of the individual, and could put themselves easily into the individual's place. Medical men were trained to sift the real from the unreal, and were as likely to achieve truth and justice as any other body of people. Sir HUGH LINSTEAD (Putney, Con.) held that the balance of advantage rested clearly in favour of the Bill with the amendment. Once they had settled down the tribunals would act in a satisfactory way. They would have judicial assessors to help them, and if they did put a foot wrong there was an ultimate right of appeal to the Judicial Committee of the Privy Council. Mr. POWELL concluded the discussion with the observation that in this amendment they were starting from the point where they had all decided that these were fit bodies to have these disciplinary powers, and were giving them the full means they required to exercise them fitly. The amendments were agreed to.

QUESTIONS IN THE COMMONS

Group Practice Loans

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) questioned the Minister of Health on October 25 about applications to the group practice loans subcommittee, asking how many were outstanding or had been rejected because the available funds were fully committed for the current year, and what was the average time between application and approval. Mr. ENOCH POWELL informed him that the available funds were not yet fully committed. In the financial years 1957–8, 1958–9, and 1959–60 funds were fully committed four, five and a half, and six months respectively before the end of the year, but the committee continued to approve applications for loans during those months subject to the proviso that money might not be available until the beginning of the following year. The average lapse of time between the committee receiving an application and approving it was four and a half months.

Parking of Doctors' Cars

Mr. J. THORPE (North Devon, Lib.) asked what instructions had been given to traffic wardens about cars parked by doctors who were in the course of discharging

their professional duties. Mr. D. RENTON, Under Secretary, Home Office, replied that he was informed by the Commissioner of Police, under whose directions they acted, that traffic wardens gave such consideration as might be possible in cases in which cars parked in contravention of the parking regulations were believed to belong to doctors visiting patients.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on October 13 the following degrees were conferred:

D.M.—P. D. Wall (in absence).
B.M.—Mrs. Anne Stern (in absence).

Dr. P. J. R. Phizackerley has been elected to the Oliver Gatty Fellowship in Biological Sciences at Balliol College.

UNIVERSITY OF CAMBRIDGE

In Congregation on October 15 the following degrees were conferred:

M CHIR.—R. C. Shepherd.
M.B., B.CHIR.—*K. A. Macdonald-Smith, *A. M. D. Mitchell.
M.B.—*J. P. Watson, *P. R. C. Steele, *M. I. J. Andrews, *R. D. B. Leicester, M. E. Snell.

*By proxy.

UNIVERSITY OF LEEDS

The degree of Ph.D. in Medicine was awarded to Julian Wladislaw Czerkawski in September.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At the annual meeting of the College, held on October 19, the following officers were elected: *President*, Professor John Bruce; *Vice-presidents*, Professor Norman M. Dott and Mr. Walter W. Galbraith; *Secretary*, Mr. James A. Ross; *Treasurer*, Mr. J. J. Mason Brown; *Representative on General Medical Council*, Mr. K. Paterson Brown; *Conservator of Museum*, Professor Eric C. Mekie; *Honorary Librarian*, Sir Walter Mercer.

The following candidates, having passed the requisite examinations, were admitted Fellows:

R. H. Ahmed, R. G. Asghar, S. A. Askari, M. P. Awon, M. Balasegaram, Fiona M. Bennett, R. K. Berry, D. E. Burgess, C. W. P. Canagaretna, D. B. Chapman, S. D. Clarke, J. Ll. Colvin, J. Y. Crooks, R. B. Davey, V. Dawle, J. A. S. Dickson, T. S. Doss, E. I. P. Ebosie, E. A. Elebute, S. K. Ghose, S. D. Gupta, U. C. Gupta, Khin Maung Gyi, K. I. M. Heath, G. S. Hiremath, R. S. Hole, D. Hugo, J. A. Hyde, J. O'H. Hyde, H. B. S. Kemp, I. R. Kernohan, I. T. Kubchandani, R. P. Kumar, J. B. Laine, R. A. Leggatt, Greta I. Leitch, Franklin Wang-Pong Li, G. Low, Earl Ming-Teh Lu, D. J. McAuliffe, Jean M. M. McKenzie, J. H. McKessar, M. P. Manomohan, M. A. K. M. Mansour, M. D. Middleton, L. J. Phillips, P. A. M. Pozzi, N. M. Prabhu, K. A. Ramalingam, M. V. Ramchandani, V. D. Raval, D. M. Ritchie, A. Sarsam, I. G. Schraibman, A. Simpson, J. W. Smith, M. G. H. Smith, D. D. Sumariwalla, G. R. Thoms, R. S. Todd, P. J. Venter, J. P. A. Weaver, D. G. Wray, I. W. M. Wright, J. Yogaratnam

ROYAL FACULTY OF PHYSICIANS AND SURGEONS

At a meeting of the Faculty held on October 3, with the President, Mr. Arthur Jacobs, in the chair, the following were admitted Fellows of Faculty: *qua Physician*, J. H. Dagg; *qua Surgeon*, P. P. Reddy, N. V. Sweeney.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At the meeting of the Council of the College held on September 24, with the President, Sir Andrew Claye, in the chair, the following were admitted to the Membership:

A. A. Armar, C. Bam, D. N. Banerjee, S. K. Banerjee, N. MacG. D. Blyth, Pauline M. Bousquet, A. H. Bradfield, G. F. Bradfield, I. T. Brake, T. Busuttil, I. E. Cary, K. L. Collins, Joan M. Curtis, L. S. Deane, Maric T. D'Netto, R. F. Heys, Ma Hla-Kyi, Florence P. Isaiah, W. I. H. Johnston, J. B. Jones, K. Kanakadurramba, W. Kelso, J. F. Kemp, J. F. Leeton, J. L. Marcus, J. M. Mistry, W. M. Moore, E. D. Morris, B. K. Mukherji, O. A. Ojo, P. R. B. Pedlow, W. S. E. Perera, W. Pollard, Doreen Rothman, A. K. Sinha, S. J. Smal, A. M. Smith, H. J. Solomon, B. Sutherland, T. E. Torbet, A. R. Trist, W. L. Whitehouse.

SCOTTISH TRIPLE QUALIFICATION BOARD

The following candidates have passed the final examinations and have been granted the diploma of L.R.C.P.Ed., L.R.C.S.Ed., L.R.F.P.&S.Glas.: E. B. Gonzalez, J. O. Djan, H. H. Grosser, M. N. Kaleel, J. O. Mojola, T. S. Twyble.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

At a primary examination for the Fellowship of the College held in Melbourne, Sydney, and Dunedin in September the following candidates were approved:

P. B. Brown, J. A. Buntine, H. Byrne, A. B. G. Carden, G. M. Clark, R. R. S. Colman, D. M. Conroy, T. W. Doous, M. H. Ellis, N. G. Graham, J. May, B. J. Parker, G. E. Scarf, B. D. Shepherd, R. G. H. Talbot, Francis Khin-Yoong Thong, I. H. Wilson.

At a primary examination for the Fellowship of the Faculty of Anaesthetists of the College held in Melbourne, Sydney, and Dunedin in September the following candidates were approved:

M. J. Kirwan, T. L. O'Connell, J. J. O'Leary, Agnes E. Sinclair, N. C. Wimsett.

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending	
Measles	Oct. 15	Oct. 22
Lancashire	1,072	**1,234**
Liverpool C.B.	152	**159**
Manchester C.B.	62	**136**
Yorkshire West Riding	311	**401**
Bradford C.B.	88	**127**
Dysentery		
Gloucestershire	35	**20**
Bristol C.B.	7	**18**
Lancashire	84	**82**
Liverpool C.B.	18	**27**
London	89	**67**
Finsbury	12	**11**
Lewisham	5	**13**
Southwark	20	**17**
Middlesex	31	**30**
Southgate M.B.	5	**13**
Surrey	45	**33**
Epsom and Ewell M.B.	32	**22**
Yorkshire North Riding	25	**21**
Middlesbrough C.B.	21	**21**
Yorkshire West Riding	66	**56**
Leeds C.B.	28	**29**
Glasgow	144	**117**
Diphtheria		
London	0	**3**

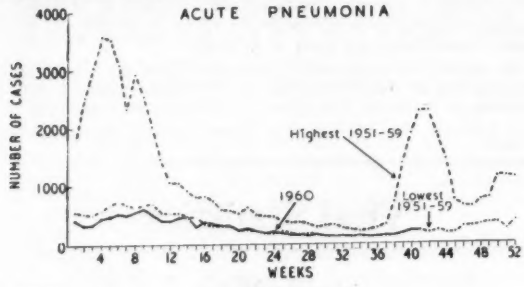
Births and Deaths in the Third Quarter

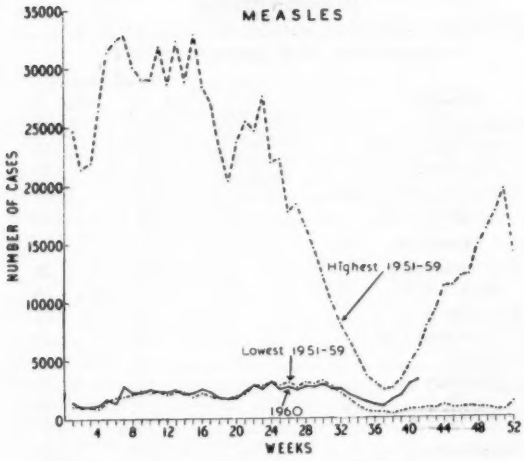
Provisional figures issued by the Registrar-General show that during the third quarter of 1960 the birth rate was higher and the death rate lower than during the same quarter last year. At 17.2 per thousand population the birth rate was the highest for any third quarter since 1948, when it was 17.5. The figures for 1959 and 1958 were 16.3 and 15.9 respectively. The death rate of 9.8 per thousand population compares with 9.0 (1959) and 9.3 (1950). The infant mortality rate was 18.8 per thousand live births. This is the lowest figure recorded during a third quarter: last year it was 19.4 and in 1950 it was 23.9. The stillbirth rate of 19.2 per thousand live and stillbirths compares with the 1959 figure of 20.5 and the 1950 figure of 22.5—*The Registrar-General's Weekly Return for England and Wales*, 1960, No. 42.

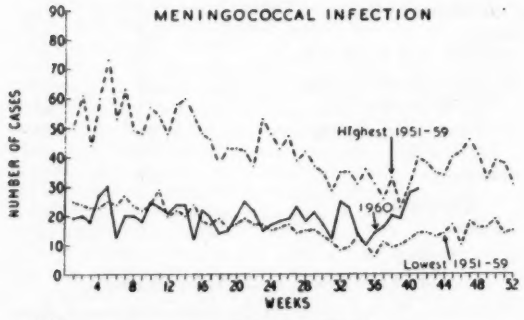
Graphs of Infectious Diseases

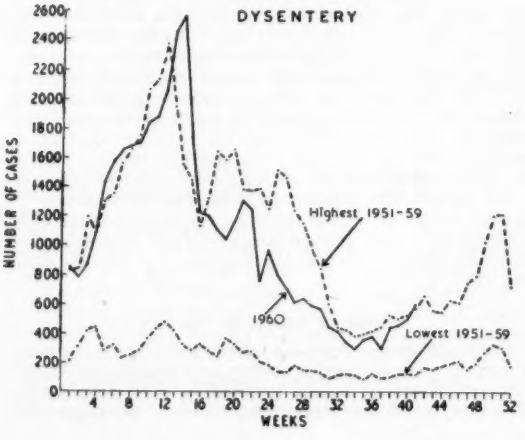
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for

1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 15** (No. 41) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	4	0	0	0		5	4	4	0	
Dysentery	600	89	204	10	6	460	37	265	6	7
Encephalitis, acute	4	0	0	0		3	0		0	
Enteric fever:										
Typhoid	1	0	1	1		4	0	0	0	
Paratyphoid	12	1	0	0	2	6	0	1(B)	0	2(B)
Food-poisoning	188	19	24	3		248	19	15	0	
Infective enteritis or diarrhoea under 2 years				20	28				21	37
Measles*	3,210	173	59	7	13	959	25	17	39	60
Meningococcal infection	29	2	7	0	1	21	0	9	1	1
Ophthalmia neonatorum	24	2	4	0		15	3	3	0	
Pneumonia†	239	15	137			252	19	119	0	
Poliomyelitis, acute:										
Paralytic	8	0	0	2	8	18	1	0	2	4
Non-paralytic	7	0	0			5	2	2		
Puerperal fever§	201	42	9	0		216	26	15	2	
Scarlet fever	424	28	74	27	18	918	46	123	28	28
Tuberculosis:										
Respiratory	426	57	72	14		424	52	60	18	
Non-respiratory	49	3	16	5		53	5	12	5	
Whooping-cough	933	90	91	10	29	502	35	100	4	28

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	2	1	0	2	5	0	0	1	0
Influenza	17	1	0	1	0	11	0	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	464	41	22	12	10	356	28	17	6	6
Poliomyelitis, acute	4	0		0	0	3	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	67	4	4	2	4	71	5	3	2	0
Non-respiratory		0	0	0	0		0	2	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	304	35	27	12	9	193	33	27	7	7
Deaths (excluding stillbirths)	9,572	757	533	113	184	8,339	631	500	118	143
LIVE BIRTHS	15,064	1233	1005	264	483	14,182	1185	1012	240	358
STILLBIRTHS	274	18	22			270	18	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

B.M.A. Scientific Exhibition, 1961

The Association's Annual Representative Meeting, followed by a Clinical Meeting, is to be held next year in Sheffield from July 17 to 22. There will be a Scientific Exhibition in the City Hall throughout the Meeting. Those who wish to exhibit should apply for a stand as soon as possible. The hall is a small one and only portable stands will be available; there will be no wall stands as in previous years, and large apparatus cannot be displayed. Certificates of merit will be awarded to the exhibits judged to be of the highest teaching value and of the highest scientific value, and the Lawrence Abel Cup will be presented for the most outstanding exhibit. Application forms for space at the Exhibition are obtainable from the Secretary, B.M.A. House, Tavistock Square, London W.C.1. The closing date for applications is December 31.

Wellcome Trust Grants

During the six months from March 1 to August 31 this year the Wellcome Trustees made the following major grants to assist medical research. Together with smaller grants totalling £41,000, and Wellcome Research Travel Grants totalling £17,000, the allocations by the Trustees in this period exceeded £420,000:

Middlesex Hospital Medical School, University of London: £50,000 for a suite of Wellcome Research Laboratories in the pharmacology department of the new Medical School building. *Massachusetts General Hospital, Boston, U.S.A.:* £50,000 to establish a Wellcome research professorship for 10 years.* *Medical Research Council:* (1) £61,000 to construct a laboratory and housing accommodation for an epidemiological research unit in Jamaica. (2) £60,000 to provide five Sir Henry Wellcome Research Travelling Fellowships for five years.* *McGill University, Montreal, Canada:* £40,000 to extend the support of the Wellcome research department of anaesthesia for a further five years. *University of Pennsylvania, Philadelphia, U.S.A.:* £17,000 to extend the support of the Wellcome associate professorship of research in anaesthesiology for a further three years. *Trinity College, Dublin:* £16,000 to construct and equip an experimental surgery unit and an animal house. *Oxford University:* £16,300 to construct an animal house for the use of workers in the department of the Regius professor of medicine. *Postgraduate Medical School, University of London:* £6,000 to equip a cardiac catheterization research laboratory in the department of medicine. *University of Birmingham, Department of Biochemistry:* £10,000 for equipment to study the nature and functions of the proteins of brain and muscle. *St. Mary's Hospital Medical School, University of London:* £8,500 for an analytical ultracentrifuge to study the structure of antigens and antibodies. (* Already announced.)

In addition the Trustees made grants totalling £21,800 for special research apparatus of various kinds. A grant of £1,000 to purchase special equipment for high-altitude research was made to Dr. L. G. C. E. PUGH, physiologist to the Himalayan Scientific and Mountaineering Expedition, 1960–61.

Royal College of Surgeons of Edinburgh

Professor JOHN BRUCE has been re-elected President and Professor N. M. DOTT and Mr. W. W. GALBRAITH Vice-presidents for the coming year.

New M.R.C. Research Units

The Medical Research Council have recently established the following new research units: the Gastroenterology Research Unit at the Central Middlesex Hospital under the direction of Dr. E. N. ROWLANDS, and the Unit for Research on the Chemical Pathology of Mental Disorders in the department of physiology at Birmingham University under the honorary direction of Professor I. E. BUSH.

Society of Chiropodists

The Society of Chiropodists has issued a statement welcoming the recognition given to qualified chiropodists by the passing of the Professions Supplementary to Medicine Bill. This provides for a State Register of Chiropodists, and, while registration is not compulsory, those who are not registered will be unable to undertake work in the National Health Service or with a local health authority. The Society estimates that there are at present between 8,000 and 10,000 people who call themselves chiropodists, less than half of whom are qualified in accordance with Government regulations. (See annotation at p. 1375.)

Chair of Surgery, St. Mary's Hospital Medical School

Mr. W. T. IRVINE, reader in surgery at London Hospital Medical College, has been appointed to the University chair of surgery tenable at St. Mary's Hospital Medical School.

After qualifying B.Sc. in 1944, and M.B., Ch.B. in 1947 at Glasgow University, Mr. Irvine held house appointments at the Western Infirmary, Glasgow. Then followed periods in the British Postgraduate Hospitals at Hammersmith and at Warrington. After obtaining his F.R.C.S.Ed. in 1950, he entered the R.A.M.C. and was for two years surgical specialist at Hamburg Military Hospital. He obtained his F.R.C.S.Eng. in 1952. On demobilization he returned to the Western Infirmary, Glasgow, for a year. In 1955 he was appointed Archibald Fellow in Surgery at McGill University, Montreal, and in 1956 was Mayo Foundation Fellow in Physiology for a year at the Mayo Clinic, Rochester, Minnesota. During these years he published work on the aetiology of hyperchloraemic acidosis after ureteral transplantation and the role of histamine in acid secretion. He returned in 1956 to hold the lectureship in surgery at the Western Infirmary, Glasgow. He obtained his Ch.M. (Honours) in 1956 and M.D. (Honours) in 1957. In 1957 he was appointed to his present position. While at the London Hospital he has published papers on various aspects of gastroenterology. He has recently introduced into this country the method of isolated limb perfusion using cytotoxic agents in the treatment of advanced tumours.

College of G.P.s' Public Welfare Foundation Prize

The College of General Practitioners is offering to senior medical students in the United Kingdom and Eire six Public Welfare Foundation Prizes of £40 each for a case history, with a suitable commentary, of one or more patients seen in general practice. Details and application forms may be obtained from the dean of the student's medical school or from the Secretary of the College of General Practitioners, 41 Cadogan Gardens, London S.W.3. The closing date for the competition is May 1. This year, the fourth year in which the competition has been held, there were 43 entries representing 14 medical schools.

"Journal of the Forensic Science Society"

The Forensic Science Society, which was founded on October 31 last year (see *Journal*, November 14, 1959, p. 1031), has now issued the first number of the *Journal of the Forensic Science Society*; this will be published twice yearly in September and March. It will cover all aspects of forensic science—research and applied, civil and criminal—and its editor is Mr. S. S. KIND, B.Sc., F.L.S., M.I.Biol. Manuscripts and other communications should be addressed to him at *Journal of the Forensic Science Society*, c/o ROSSETT HOLT, Pannal Ash Road, Harrogate, Yorkshire, England. The subscription is £2 a year, post free.

"Medicine, Science, and the Law"

The British Academy of Forensic Sciences (see *Journal*, November 7, 1959, p. 965) is publishing the first issue of its quarterly journal, *Medicine, Science, and the Law*, in October, and thereafter in January, April, and July. The journal is directed generally to anyone concerned with medicine, science, and the law, but particularly to anaesthetists, biochemists, biologists, chemists, coroners, members of forensic science laboratories, lawyers, pathologists, police forces, police surgeons, prison medical officers, psychiatrists, and zoologists. The editor is Dr. F. E. CAMPS, and manuscripts should be sent to him at the publishers, *Medicine, Science, and the Law*, Sweet and Maxwell, Ltd., 11 New Fetter Lane, London E.C.4. The subscription is £3 3s. a year.

Medical Protection Society

Sir CLEMENT PRICE THOMAS has been elected president of the society in succession to the late Sir ERNEST ROCK CARLING.

Change of Address

The new address of the National Council for the Unmarried Mother and Her Child (Inc.) will be 255 Kentish Town Road, London N.W.5 (Tel.: general—Gulliver 8166; case department—Gulliver 9130), from November 21.

The new address of the *Postgraduate Medical Journal* is Fellowship of Postgraduate Medicine, 9 Great James Street, London W.C.1. (Tel.: CHAncery 6900.)

Grants, Gifts, and Bequests

The Nuffield Foundation is to award two scholarships in tropical medicine to enable two senior medical students of Birmingham University to visit the medical school at University College, Ibadan.

In Brief

A contributory health service has been approved in principle by the States of Jersey.

Budapest City Council is to spend about £3m. on building and equipping a new 500-bed hospital in the South Pest part of the city. It should be completed by the autumn of 1965.

People in the News

Dr. A. S. PARKES, Sc.D., F.R.S., has been appointed Mary Marshall Professor of the Physiology of Reproduction at Cambridge University from October 1 this year.

Dr. W. B. J. PEMBERTON is the new editor of the *Catholic Medical Quarterly*.

During a recent visit to the United States Sir HARRY PLATT gave the Edward Holman Skinner Memorial Lecture before the Kansas City Southwest Clinical Society, his subject being "Whither Medicine?"

During a visit to the U.S.A. in November Mr. TERENCE CAWTHORNE will take part in a symposium on otosclerosis at the Henry Ford Hospital, Detroit, and will give lectures to the Academy of Medicine, Toronto, the Jefferson Medical College, Philadelphia, and the Houston Otolaryngological Society.

COMING EVENTS

Society for Psychosomatic Research.—Conference, "Psychosomatic Disorders. — Adolescents and Young Adults," November 11–13, Royal College of Physicians. Details from Dr. H. H. WOLFF, 26 Welbeck Street, London W.1.

Langdon-Brown Lecture, R.C.P. London.—Professor D. V. HUBBLE, "The Endocrine Orchestra," November 17. For details see advertisement p. 73.

College of General Practitioners.—Symposium, "Mental Health and the Family Doctor," November 20, Wellcome Building, Euston Road, London N.W.1. 10 a.m.: "Emotional Disorders—General Practice" (chairman, President College of General Practitioners); 2.10 p.m.: "The Psychoses in General Practice" (chairman, Sir AUBREY LEWIS). Details from the College, 41 Cadogan Gardens, Sloane Square, London S.W.3.

University of London.—Professor C. E. LUMSDEN, "The Pathology and Pathogenesis of Multiple Sclerosis," November 21, 5.30 p.m., London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London W.C.1. Admission free.

4th (Annual) Ciba Foundation Lecture on Research on Ageing (in conjunction with meetings of British Society for Research on Ageing and British Geriatrics Society).—Dr. P. J. THUNG (Antoni van Leeuwenhoek-Huis, Amsterdam): "Ageing in the Gonad-Adrenal System," November 24, 5 p.m., Arthur Thomson Hall, Medical School, Edgbaston, Birmingham. Chairman: Sir SOLLY ZUCKERMAN, F.R.S. No fee or ticket.

"Health of Executives."—Conference, November 24, Royal Festival Hall, London. Details from Chest and Heart Association, Tavistock House, London, W.C.1.

British Society for Immunology.—Autumn meeting, Wellcome Building, 183 Euston Road, London, N.W.1, November 25, 26. Symposium: "Stimulation of Antibody Production" (chairman, Sir JOHN BOYD, F.R.S.) on 25th, 9.30 a.m.

University College, London.—A reunion dinner at the College, February 17, for former undergraduates or postgraduates entering before 1918. Applications before December 31 to Assistant Secretary, University College London, Gower Street, W.C.1.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY

British Pharmacological Society and Scandinavian Pharmacological Society.
The Responses of the Venus Heart to Catechol Amines and High Concentrations of 5-hydroxytryptamine. M. J. Greenberg.
Structure-activity Relationship of Tryptamine Analogues on the Heart of Venus Mercenaria. M. J. Greenberg.
The Effects of Adrenaline and Noradrenaline on the Metabolism and Performance of the Isolated Dog Heart. G. Fawaz and B. Tutunji.
The Anti-Anaphylactic and Histamine-Releasing Properties of the Antihistamines. Their Effect on the Mast Cells. I. Mota and W. Dias da Silva.
The Inhibition of Mast Cell Damage and Histamine Release in Anaphylaxis by Pyridine and Diphosphopyridine Nucleotidase Inhibitors. Comparison with Compound 48/80. Ivan Mota, W. Dias da Silva, and Fernandes J. Ferreira.
The Isolated Chick Biventer Cervicis Nerve-muscle Preparation. B. L. Ginsberg and Joan Warriner.
A New Biological Method for the Assay of Depolarizing Substances Using the Isolated Semispinalis Muscle of the Chick. K. J. Child and Eleanor Zaimis
The Release of Acetylcholine from Mammalian Motor Nerve Endings. D. W. Straughan
The Inhibition by Morphine of the Action of Smooth Muscle Stimulants on the Guinea-pig Intestine. G. P. Lewis.
Maximal Inhibition of Cholinesterase in the Central Nervous System. W. Schaumann.
Screening of Cesticidal Compounds on a Tapeworm Hymenolepis Nana in vitro. A. B. Sen and F. Hawking.
Pharmacological Activity of an Aqueous Extract of the Leaves of the Malayan Rengas Tree Gluta Renghas. R. C. Y. Lin and G. C. Whittow.
The Response of Isolated Rabbit Atria to Aconitine. John Yelnosky and Byron B. Clark.
Anaesthesia in New-born Animals. Josephine A. C. Weatherall.
Experiments on the Pharmacology of Hydroxydione Sodium Succinate. L. H. Lerman and W. D. M. Paton.
Peripheral Vascular Effects of Bretylium Tosylate in Man. D. A. Blair, W. E. Glover, B. S. L. Kidd, and I. C. Roddie.
The Antagonism of Muscle Relaxants by Ambenonium and Methoxyambenonium in the Cat. L. C. Blaber.

Volume 15, No. 3. (Quarterly: £4 4s. annually.)

GUT

Post-gastrectomy Syndromes: A Review. C. F. W. Illingworth.
The Use of Cholecystokinin to Test Gall Bladder Function in Man. P. Burton, A. A. Harper, Henry T. Howat, J. E. Scott, and H. Varley.
Gastric Cytodiagnosis: A Review and Appraisal. D. D. Gibbs.
An Assessment of Prednisone, Salazopyrin, and Topical Hydrocortisone Hemisuccinate Used as Out-patient Treatment for Ulcerative Colitis. J. E. Lennard-Jones, A. J. Longmore, A. C. Newell, C. W. E. Wilson, and F. Avery Jones.
A Clinical and Statistical Study of the Effect of Gastrojejunostomy on Human Gastric Secretion. H. I. Tankel, I. E. Gillespie, D. H. Clark, A. W. Kay, and J. McArthur.
A Comparison Between the Effects of Hexamethonium and Atropine in Combination and of Vagotomy with Gastrojejunostomy on Human Gastric Secretion. J. McArthur, H. I. Tankel, and A. W. Kay.
Massive Reaction of the Small Intestine after Occlusion of the Superior Mesenteric Artery. R. J. Harrison and C. C. Booth.
Factors Influencing the Growth of Staphylococcus aureus in the Stomach after Gastric Operations. F. G. Smiddy and D. Pratt.
Gastric Activity in the South African European and Bantu. I. Macdonald.
Benign Duodeno-colonic Fistula. G. N. Chandler and A. J. Longmore.
Surgery in Bleeding Peptic Ulcers. J. N. Ward-McQuaid, J. C. Pease, A. McEwen Smith, and R. J. Twort.
New Methods for Diagnosis and Research. Wireless Telemetering from the Digestive Tract. A. M. Connell and E. N. Rowlands.

Volume 1, No. 3. (Quarterly; £3.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 7

MARLBOROUGH DAY HOSPITAL.—8.15 p.m., Dr. Denis Leigh: Teaching of Psychotherapy.

POSTGRADUATE MEDICAL SCHOOL.—4 p.m., Dr. Brian Ackner: Diagnosis of Depressive Illness.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. A. S. Todd: Fibrin and Fibrinolysis.

Tuesday, November 8

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., joint meeting with Midland Branch of British Psychological Association. Mr. Malcolm Piercy: Psychological Theories in Psychiatry and Neurology.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. W. M. Court Brown: Chromosome Analysis and Clinical Medicine.

COLLEGE OF GENERAL PRACTITIONERS: EAST LONDON FACULTY.—At Anatomy Theatre, London Hospital Medical College, 8.30 p.m., Pfizer Lecture by Professor J. N. Morris: Research in Cardiovascular Disease.

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Provision for the Training of Mentally Handicapped Children in Day Centres. Speakers: Dr. M. Sheridan, The Young Child; Mrs. W. M. Curzon, The Junior Group. A discussion will follow.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: Anomalies of Pigmentation.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Paul Sandifer: Involuntary Movements in Children.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Clinical Sciences Building, York Place, 7.30 for 8 p.m., Mr. A. Jolleys: Treatment of Peripheral Tuberculous Glands; Dr. H. B. Andrews: Tuberculous Glands.

METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL.—At Rushcliffe House, St. Mary Abbots Hospital, 5.30 p.m., Mr. R. Scott Stevenson: Vertigo.

ST. ANDREWS UNIVERSITY.—At Anatomy Department, Lecture Theatre, 5 p.m., Dr. J. D. B. Macdougall: Methods in Tissue Culture (II).

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Mr. D. G. Bonham: Non-Malignant Enlargement of the Ovary.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. T. Rowland Hill: Neurology.

Wednesday, November 9

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Skin Cancer.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Paul Wood: Present Position of Anticoagulant Therapy in Cardiovascular Disease.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. K. Vernon: Cancer of the Kidneys.

●LEEDS UNIVERSITY.—At General Infirmary at Leeds, (1) 5 p.m., Miss Ursula M. Lister: Placenta. (2) 6 p.m., Mr. T. F. Redman: Inefficient Uterine Action.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Charles Wilcocks: Aspects of Medical Investigation in Africa—Trypanosomiasis.

MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Manchester University Medical School, 4.30 for 5 p.m., Dr. L. Poller: Pathogenesis of Thrombosis.

POSTGRADUATE MEDICAL SCHOOL.—2 p.m., Dr. P. J. Rendle: Regulation of Carbohydrate Metabolism by Hormones and Other Factors.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., Frederick Price Lecture by Lord Cohen of Birkenhead: Changing Concepts of Diathesis in Medicine.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. A. W. McKenny-Hughes: Household Insects.

ROYAL SOCIETY OF HEALTH.—At 90 Buckingham Palace Road, S.W., 2.30 p.m., symposium by Dr. B. W. Robinson, Ph.D., Professor W. Burns, and Dr. T. W. Parker, Ph.D.: Noise—Its Causes, Effects, and Abatement.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. R. S. McNeill: Different Aspects of Lung Function.

YORKSHIRE SOCIETY OF ANAESTHETISTS.—At General Infirmary at Leeds, 8.15 p.m., symposium by Dr. R. P. Harbord, Dr. Gwendolen Harrison, and Dr. F. G. Mackintosh: North American Anaesthetic Scene.

Thursday, November 10

ALFRED ADLER MEDICAL SOCIETY.—At 11 Chandos Street, London W., 8 p.m., Mr. Lewis Way: Some Problems of Social Psychology.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. M. R. Pollock: Physiological Adaptation in Micro-organisms.

CHILTERN MEDICAL SOCIETY.—At Amersham General Hospital, 8.30 p.m., clinical meeting.

GROUP FOR REPRESENTATION OF VIEWS OF CLINICAL PSYCHIATRISTS.—At Private Room, Tavistock House North (Fourth Floor), Tavistock Square, W.C., 5.30 p.m., committee meeting.

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Mr. J. H. S. Scott: Accident Services—A Review of Current Trends.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Dr. Charles Wilcocks: Aspects of Medical Investigation in Africa—Implications.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Watson-Jones Lecture by Dr. P. A. Wade: Accident Surgery of Motorways.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor M. F. A. Woodruff: Outlook for Transplantation of the Kidney in Man.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: postgraduate demonstration in neurology.

Friday, November 11

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. C. W. MacFarlane: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Dr. D. A. Osborn: Disorders of Blood in E.N.T. Practice.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., Brains Trust on Paediatric Anaesthesia. Chairman, Dr. J. B. Hargreaves. Panel, Professor T. C. Grey, Dr. R. W. Cope, Dr. R. M. Smith, and Dr. G. J. Rees.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. A. J. C. Latchmore: Surgery of Biliary Tract. (2) 4 p.m., Professor W. S. Peart: Ischaemic Kidneys in Hypertension.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. R. S. McNeill: Common Tests of Lung Function and their Application.

YORKSHIRE THORACIC SOCIETY.—At Instructional Block, General Infirmary at Leeds, 5.30 p.m., Dr. Graham Hayward: Pulmonary Oedema.

Sunday, November 13

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE.—At Theatre 1, Clinical Sciences Building, York Place, Manchester, 11 a.m., in conjunction with North-west England Faculty, College of General Practitioners. Dr. D. Longson, Dr. A. W. Davison, and a dietitian: Diabetes.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—A. J. Smith, M.D., D.Path., Part-time Consultant Pathologist, and M. S. N. Pathy, Whole-time Consultant Physician (Geriatrics) to Coventry group of hospitals; D. W. Stuart, M.B., B.S., F.R.C.S., F.R.C.S.Ed., D.L.O., Part-time Consultant Ear, Nose, and Throat Surgeon to Stoke-on-Trent group of hospitals; I. A. Kellock, M.D., M.R.C.P., Whole-time Consultant Physician (Geriatrics), and W. D. Foster, M.D., Whole-time Consultant Pathologist to Birmingham (Dudley Road) group of hospitals; Patricia M. Lumb, M.B., Ch.B., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist to United Birmingham Hospitals and Birmingham (Selly Oak) and Birmingham (Sanatoria) groups of hospitals.

MANCHESTER REGIONAL HOSPITAL BOARD.—R. Dowie, M.B., Ch.B., M.R.C.O.G., Consultant Obstetrician and Gynaecologist (eight half-days weekly), Barrow and Furness Group of Hospitals; A. H. Swithinbank, M.B., Ch.B., F.R.C.S., D.A., Consultant General Surgeon (eight half-days weekly), Wigan and Leigh Group of Hospitals; I. M. Hallack, M.B., Ch.B., F.F.A. R.C.S., D.A. Consultant Anaesthetist (nine half-days weekly), Salford Group of Hospitals; I. W. Davidson, M.B., Ch.B., F.F.A. R.C.S., D.A., Consultant Anaesthetist (nine half-days weekly), North Manchester, Booth Hall, and Monsall Groups of Hospitals; W. J. Ross, L.R.C.P., L.R.C.S.Ed., L.R.F.P.S., Whole-time Senior Casualty Officer, Victoria Hospital, Blackpool; R. M. Peck, L.A.H., Whole-time Senior Casualty Officer, Royal Albert Edward Infirmary, Wigan; J. M. Brown, M.B., Ch.B., F.F.R., D.M.R.D., Whole-time Consultant Radiologist, Preston and Chorley group of hospitals; T. Lyall, M.D., Whole-time Consultant Venereologist, Stockport and Buxton. Macclesfield and District, South Cheshire and Salford groups of hospitals; E. H. Wilson, M.D., Consultant Geriatrician, Lancaster and Kendal and Lancaster Moor groups of hospitals; L. Doyle, M.B., B.Ch., M.R.C.P.I., D.C.H., Whole-time Consultant Chest Physician, South Manchester group of hospitals; G. H. Elldige, M.B., Ch.B., M.R.C.O.G., D.Obst.R.C.O.G., Consultant Obstetrician and Gynaecologist, Bury and Rossendale group of hospitals; R. K. Gilbert, F.D.S., L.R.C.P.&S.I., Whole-time Senior Hospital Dental Officer, South Manchester group of hospitals; T. Loughnane, M.B., B.Ch., D.P.H., D.P.M., Whole-time Assistant Psychiatrist, Whittingham Hospital, near Preston; L. W. Carstairs, M.D., M.R.C.P., Consultant Chest Physician, Burnley and District group of hospitals; A. J. Sims, M.B., B.S., F.F.A. R.C.S., D.A., Consultant Anaesthetist, Bury and Rossendale group of hospitals; V. J. E. Davies, B.M., B.Ch., Assistant Pathologist, Oldham and District group of hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Acheson.—On October 11, 1960, at Guy's Hospital, London S.E., to Fiona (formerly O'Brien), wife of Dr. Roy M. Acheson, a son—Vincent Rennoldson.

DEATHS

Biggane.—On October 6, 1960, Edward Fitzgerald Biggane, M.B., B.Ch., of Stowe-on-the-Wold, Cheltenham, Glos, formerly of Bolton, Lancs.

Blake.—On October 14, 1960, Harold Henry Blake, O.B.E., M.B., B.S., Major-General, late R.A.M.C., retired, of Surrey Lodge, Brockenhurst, Hants, aged 77.

Butler.—On October 8, 1960, Elizabeth Fraser Butler, M.D., D.P.H.

Draper.—On October 16, 1960, at Sacramento, California, U.S.A., Rue William Draper, M.B., F.A.C.S.

Furber.—On October 17, 1960, Lionel Gipps Hopkins Furber, L.M.S.S.A., of Twyford, Berks, aged 82.

Mayer.—On October 1, 1960, at Floréal, Mauritius, Clifford Antony Leo Mayer, M.D., D.T.M.&H.

Mitchell.—On October 9, 1960, Charles Edward Sawers Mitchell, M.B., Ch.B., of 34 Cotswold Gardens, Hendon Way, London N.W., late of British Guiana, aged 84.

Parrott.—On October 9, 1960, at Odstock Hospital, Salisbury, Wilts, John Norman Parrott, M.R.C.S., L.R.C.P., of Avon Gorse, Hurn Road, Ringwood, Hants, late of Hayes, Middlesex.

Pearson.—On September 21, 1960, George Harold Pearson, M.B., B.S., D.P.H., of Port Elizabeth, late of Kimberley, South Africa.

Pinkerton.—On October 9, 1960, at sea, John McLean Pinkerton, *M.C.*, M.B., F.R.C.S., of Bath, Somerset, and Auckland, New Zealand.

Pritchard.—On October 11, 1960, at his home, 59 Wood Vale, London N., Sydney Clifford Pritchard, O.B.E., M.D.

Rosenthall.—On October 8, 1960, Michael John Rosenthall, B.M., B.Ch., D.P.M., of London W., formerly of Leeds.

Sansom.—On October 11, 1960, Shirley Vivian Sansom, M.R.C.S., L.R.C.P., of Canadia House, Battle, Sussex.

Sutcliffe.—On October 7, 1960, Alan Lee Sutcliffe, M.D., of St. Martin's, Minehead, Somerset.

Terry.—On October 3, 1960, at his home, Evanston, Illinois, U.S.A., Richard Barratt Terry, M.D., M.R.C.P.

Thomson.—On October 8, 1960, at Oslo, Graham Murray Thomson, M.D., M.R.C.P.Ed., D.P.H., of 11 Bandon Road, Girton, Cambridge, and Hong Kong.

White.—On October 8, 1960, at Hammersmith Hospital, London W., Ernest Ian Hutton White, M.B., Ch.B., of Thrapston, Northants, aged 72.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Antihistamines and the Pupils

Q.—*Can antihistamines produce pupillary anomalies?*

A.—When taken orally antihistamine drugs do not have any appreciable effect on the pupils. Certain antihistamines —for example, diphenhydramine and tripelennamine—have weak atropine-like activity and they may cause dryness of the mouth and blurring of vision. Some dilatation of the pupils might be expected, but in practice this is only observed when the drugs are applied locally to the eye. Harris, McGavack, and Elias[1] gave diphenhydramine orally in a dose of 150–400 mg. daily for from 3 to 12 weeks to 20 subjects and did not observe any change either in the pupils or in vision. When the drug was applied topically to the eye as a 0.5% aqueous solution, however, there was a definite dilatation of the pupil in 48 of 60 subjects tested. The mean increase in the size of the pupil one hour after the application of the drug was 1.9 mm. Ross[2] described 4 patients in whom blurring of vision was a prominent side-effect of therapy with tripelennamine, but the pupillary reflexes were not disturbed in any of the cases. The effects of a single dose of the majority of the antihistamines lasts for only 3–6 hours. A notable exception to this is promethazine, which has an action of 18–32 hours, but it is a drug which is not very often used in the daytime because of its rather pronounced sedative effect.

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2 Ross, J. V. M., *Amer. J. Ophthal.*, 1949, 32, 987.

Asbestos in the Wine

Q.—*Many amateur wine-makers clear their wine by filtering through asbestos pulp, but the product, though clear, can be shown to have small asbestos particles in it. Could the ingestion of these eventually cause harm?*

A.—I was unable to obtain precise information on this question. Intestinal granulomata, simulating Crohn's disease, have been produced in animals by prolonged ingestion of fine sand which entered the lymphatic vessels in the mesentery and the regional mesenteric glands, producing lymphatic congestion and oedema in the region affected. No similar lesions have been reported in human subjects, and these should have come to light had asbestos ingestion been a significant hazard or acted in a similar way.

Remissions in Asthma

Q.—*(1) How often is asthma cured (i.e., the patient has no need to take anything in the pharmacopoeia)? (2) How often is this effected by hyposensitization?*

A.—Metzger,[1] of Florida, U.S.A., in an analysis of 4,000 case reports of bronchial asthma found that with rare exceptions every patient had at some time a remission of symptoms—i.e., attacks suddenly or gradually disappearing for the time being. He gives the following figures for remissions lasting one year and more. At 5–10 years, 53%; at 10–20 years, 56%; 20–30 years, 61%; 30–40 years, 52%; 40–50 years, 51%; and 50–60 years, 32%. (Remissions are highest at 20–30 years and least at 50–60 years.) Grant[2] found that 42% of 152 students in the University of Wales who gave a history of asthma had become free of attacks. Flensborg[3] followed up 298 children, former patients at two Danish Hospitals between 1926 and 1939, and found that 40% had become free of attacks.

There is little doubt that a complete remission of symptoms for a year or more is comparatively common in asthma, especially in children and young adults. Climatic factors may possibly explain the high remission rate in Florida. Rackemann,[4] of the U.S.A., in 449 children seen and treated before the age of 13 years and followed up 20 years later, found that 71.4% had become free from attacks. He found that hyposensitization reduced the time for symptoms to clear. Unger,[5] of the U.S.A., in 122 cases of pollen asthma given hyposensitization, reported 33.6% as completely free for at least a year. In this country, Milner and Tees[6] found that in 456 asthmatics given hyposensitization, 11% were completely relieved and another 63% substantially relieved.

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2 Grant, G., *Acta allerg. (Kbh.)*, 1957, 11, 37.
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4 Rackemann, F. M., and Edwards, M. C., *New Engl. J. Med.*, 1952, 246, 815, 858.
5 Unger L., *Bronchial Asthma*, 1945, p. 403. Springfield, Illinois.
6 Milner, F. H., and Tees, E. C., *Practitioner*, 1959, 182, 585.

Anticoagulants in Retinal Vascular Disease

Q.—*What are the present-day views on the use of anticoagulants in retinal vascular disease? Are they contraindicated in, for example, retinal vein thrombosis with haemorrhages? Are they of use in diabetic retinopathy?*

A.—The main indication for the use of anticoagulants in retinal vascular disease is in cases of partial thrombosis of the retinal veins. The variability in the course of this condition in untreated cases makes the assessment of the results of treatment difficult, but in my opinion anticoagulant therapy hastens resolution and prevents extension of the thrombosis. Once started, the treatment should be continued for at least two months and possibly longer.[1] The presence of retinal haemorrhages is not a contraindication. Anticoagulant therapy is of little value in diabetic retinopathy.

REFERENCE

1 Stephenson, R. W., *Trans. ophthal. Soc. U.K.*, 1956, 76, 253.

Correction.—Mr. STANLEY AYLETT (London W.1) writes: I must correct an error in your report (October 22, p. 1226) of my contribution to the symposium on enterocolitis at the recent B.M.A. meeting in Middlesbrough. I did not state that ileorectal anastomosis should be carried out in the presence of a rectal stricture. On the contrary, I quoted this complication as constituting one of the contraindications of the operation. I am aware that after dilatation of such a rectum it is possible to restore continuity, and that such a course is advocated by certain surgeons. Except in those patients who positively refuse an ileostomy—and there are such—it is not a course that I believe should be followed, as the risk of the development of carcinoma in the fibrosed regions is one that cannot be ignored.

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